

## **Transcriptomic analysis reveals abnormal repair and remodeling in survivors of critical illness with sustained muscle weakness**

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## **List of supplementary data**

### **PDF (a single file)**

1. Supplementary Methods
2. Supplementary Figure 1.

Heatmap of correlations between co-expression module eigengenes (rows) and quantitative clinical traits (columns). The clinical traits (from left to right) are FIM motor subscore, Functional Independence Measure (motor subset score); Quads mass, quadriceps cross sectional area expressed as a percentage of age and sex matched norms determined by computerized tomography; APACHE2 score, a severity of disease classification system; MRCSS, Medical Research Council sum score (a sum score of global muscle strength); Quads strength, quadriceps strength determined by quadriceps peak torque (% predicted); RIN, RNA integrity number. Scale bar (right) indicates the range of possible correlations from positive (red, 1) to negative (green, -1).

3. Supplementary Figure 2.

Enrichment Map results of the gene set functional enrichment analysis for (a) module 1 and (b) module 3. A node in the Enrichment Map

represents a gene set. Node size represents gene set size. Node color, blue or red, indicates whether gene sets are down- or up-regulated compared to controls, respectively.

4. Supplementary Table 1

Patient demographic and clinical data

5. Supplementary Table 2

Differentially expressed genes (N = 744 unique probes corresponding to 695 genes). LIMMA global analysis of differentially expressed genes between ICUAW and controls for both day 7 post-ICU and month 6 post-ICU at false discovery rate (FDR) 5% level was performed using data adjusted for age, sex, and correlation between patient samples.

6. Supplementary Table 3

Enrichment analysis of 347 genes differentially expressed (downregulated in ICUAW post-ICU day 7 versus controls) at FDR < 0.05.

7. Supplementary Table 5

Association of co-expression modules with disease status

8. Supplementary Table 6

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9. Supplementary Table 7

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10. Supplementary Table 8

8a. Module conservation between modules constructed for the human sepsis with multi-organ dysfunction validation dataset compared with reference (human ICUAW). 8b. Module conservation between modules constructed for the porcine model of ICUAW compared with reference (human ICUAW). 8c. Association of module eigengene (ME) with disease status; human sepsis with multi-organ dysfunction vs controls 8d. Association of ME with disease status; porcine model of ICUAW day 5 sepsis vs. day 1 control.

**Excel**

## 1. Supplementary Table 4

Gene and kME in different modules. Module eigengene connectivity (kME), a module membership measure, for all unique Illumina probes included in the WGCNA analysis data set (N= 11,482)

## **Supplemental Methods:**

**Patient selection:** Patients were enrolled from a multi-center nested prospective study (Towards RECOVER)<sup>1,2</sup>. Patients were included if mechanically ventilated for a minimum of 1 week and were fully ambulatory and independent with activities of daily living prior to ICU admission. Exclusion criteria included any of the following: important current or pre-existing neurological injury that would preclude cognitive testing; a formal diagnosis of neuromuscular disease; non-ambulatory prior to ICU; anticipated death or withdrawal of life sustaining treatment within 48 hours; history of psychiatric illness or significant cognitive impairment with documented hospital admission; not fluent in English or French; living greater than 300 km from referral centre; physician refusal; patient or SDM (substitute decision maker) consent refusal; and no available next of kin or SDM available (if patient unable to provide consent). Additional exclusion criteria for this nested study included important current neurological injury that would preclude motor testing; known HIV, Hepatitis B or Hepatitis C infection; therapeutic anticoagulation and/or active cancer undergoing treatment.

Written informed consent was obtained from all participants or their surrogate decision makers and participants were re-consented when capacity was regained. The study protocol was approved by the University Health Network Research Ethics Board and St. Michael's Hospital Research Ethics Board. All methods were performed in accordance with the relevant guidelines and regulations within the study protocol. Banked muscle biopsy specimens previously collected from consenting healthy individuals were used as controls.

All controls had been screened by interview and self-reported the absence of malignancy, significant cardiac, pulmonary, hepatic, renal or endocrine disease.

**Outcome measures of physical function, strength and mass:** Physical functional capacity was measured using the motor component of the Functional Independence Measure questionnaire (FIM score)<sup>3</sup>. Functional Independent Measures questionnaire (FIM) provides a numerical score for cognitive and motor function that has been validated and standardized across diverse patient populations. A higher FIM score (scale 18-126) connotes better function in both domains. The motor subscore is based on the individual's ability to perform their activities of daily living (ADLs; toileting, dressing, walking, climbing stairs, eating). A healthy individual with complete and unassisted independence of ADL would achieve a maximal FIM motor subscore of 91. The measure is independent of an individual's gender or age.

Global muscle strength was assessed by the Medical Research Council Sum Score (MRCSS)<sup>4</sup>. Manual assessment of muscle strength was performed by a physiotherapist, grading muscle strength from 0 to 5, as established by the Medical Research Council. The higher the score, the stronger the muscle group, with 5 representing what is deemed by the assessor to be normal strength, taking into account the individual's sex and age. The MRC sum score is calculated by summing the total score for bilateral shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, and ankle dorsiflexion. The score for an individual with normal strength is 60.

The midthigh *quadriceps femoris* muscle cross-sectional area (CSA) was determined as previously described<sup>5</sup>. Briefly, computed tomography imaging of

the right thigh, halfway between the pubic symphysis and the inferior condyle of the femur, using a Light Speed QXi 4 slice helical scanner (General Electric, Milwaukee, WI), was performed with the subject in the supine position. Each image was 10 to 20 mm thick, and the muscle identified as tissue with a density of 40 to 100 Hounsfield units. Images were analyzed and the CSA of thigh muscle determined by a single radiologist, blinded as to the categorization of each test subject. Quadriceps was then manually traced using ImageJ software (version 1.42q, NIH, USA) by a single investigator blinded to participant categorization and the CSA calculated. The cross-sectional area of the muscle at the midsection of the thigh determined by computerized tomography (CT) was compared to age and sex matched publication based norms <sup>6,7,8,9,10</sup> and muscle mass for study subjects is expressed as a percent of the age and sex matched norms.

Quadriceps isometric peak torque (strength) was measured from maximal voluntary contractions of the knee extensors. The patient was seated on the Bidex dynamometer (Biode System 4), with the hip at 85 degrees and knee at 60 degrees of flexion. The patient performed five maximal voluntary contractions with one minute rests, according to a previously described protocol <sup>11</sup>. Peak torque was recorded in Newton-meters (Nm). Patients' peak torque was reported in absolute terms and as percentage of the predicted normal, as previously described <sup>12</sup>. Predicted Quadriceps Force in Nm = - (2.21 x age) + (55.9 x gender [female = 0, male = 1]) + (1.78 x Body weight) + 124.

All testing was conducted at 7 days and 6 months post-ICU discharge, with the exception of the Bidex measures, which were conducted solely at 6 months. For controls, the values for FIM motor subscore, MRCSS, percent predicted quadriceps isometric peak strength, and percentage of normal

quadriceps CSA were set to the normal value in a healthy population (91, 60, 100% and 100%, respectively). Descriptive statistics of patient demographic and clinical variables are shown in **Supplementary table 1**.

**Muscle sample collection:** Biopsy of the *vastus lateralis* muscle was performed under local anesthetic using a modified Bergstrom needle, as previously described<sup>13</sup>. Briefly, under sterile conditions, the skin and subcutaneous tissue overlying the lateral aspect of the distal third of the muscle were anesthetized, and a small incision was made in the outer fascial layer with a scalpel blade. The Bergstrom needle was advanced through the incision roughly 1 cm into the muscle, suction was applied as the trochar was advanced, and several pieces of muscle tissue were obtained. The needle was withdrawn under counter pressure, the skin closed with a single suture, and a pressure dressing applied. Tissue (approx. 200mg in total) was immediately sectioned with a sterile scalpel blade and pieces were processed for electron and light microscopy or flash frozen in liquid N<sub>2</sub>.

**Muscle sample staining:** Muscle biopsies were fixed in 10% buffered formalin phosphate for 24 hours at room temperature, rinsed in ethanol, paraffin embedded and sectioned (10 µm thickness) on cross section. The sections were rehydrated in a series of xylene and ethanol washes. Nuclei were stained with Weigert's haematoxylin for 8 minutes, washed in running tap water and then sections stained in picro-sirius red for one hour. Sections were then washed in two changes of acidified water, dehydrated with ethanol and xylene washes and mounted.

**Gene set visualization using enrichment map:** Enrichment map, a network-based visual representation of enriched terms that groups similar gene sets (functional terms, was performed to aid identification of functional themes (Supplementary Figure 2). Gene set functional enrichment analysis was performed using Gene Ontology (GO) biological process terms in the web-based version of gProfiler (<http://biit.cs.ut.ee/gprofiler/>). The statistical significance threshold level for GO enrichment was Benjamini and Hochberg corrected  $p < 0.05$  and only gene sets between 10 and 100 genes were used from GO. The background list for the enrichment analysis included all genes represented on the Illumina Human HT-12 v4 array with a detection  $P$  value  $< 0.05$  in at least three samples. Enrichment Map Cytoscape plugin software was used to create the enrichment map, with the parameters  $p\text{-value} < 0.005$ , correct  $p\text{-value}$  value  $< 0.05$  and “Jaccard + overlap similarity” cutoff = 0.5.

**Independent validation data sets:** Two datasets were obtained from the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus (GEO) database. *Validation dataset 1:* Human skeletal muscle (*vastus lateralis*) transcriptome in ICU patients with sepsis induced multi-organ failure (GSE13205, 13 sepsis and 8 control samples) performed on Affymetrix GeneChip HG-U133 Plus 2.0 Array <sup>14</sup>. Expression data was age and sex corrected using residuals of a linear regression model. *Validation dataset 2:* Experimental model of ICUAW in *Sus scrofa* skeletal muscle (*biceps femoris*) transcriptome containing a total of 40 samples from a series of 5-day longitudinal experiments (24 samples, GSE16348; 8 samples GSE24239; 8 samples, GSE33037) performed

on Affymetrix Porcine Genome Array <sup>15</sup>. For both validation datasets, series raw data were downloaded (Affymetrix .CEL files) and background corrected using *rma* in the *expresso* package (“average difference” summary method) without normalization then arrays from the same platform were merged together and quantile normalized. Data quality was assessed as described above. Corresponding published putative homologs of the porcine dataset were used to link probe IDs to HUGO symbols <sup>16</sup>.

## References

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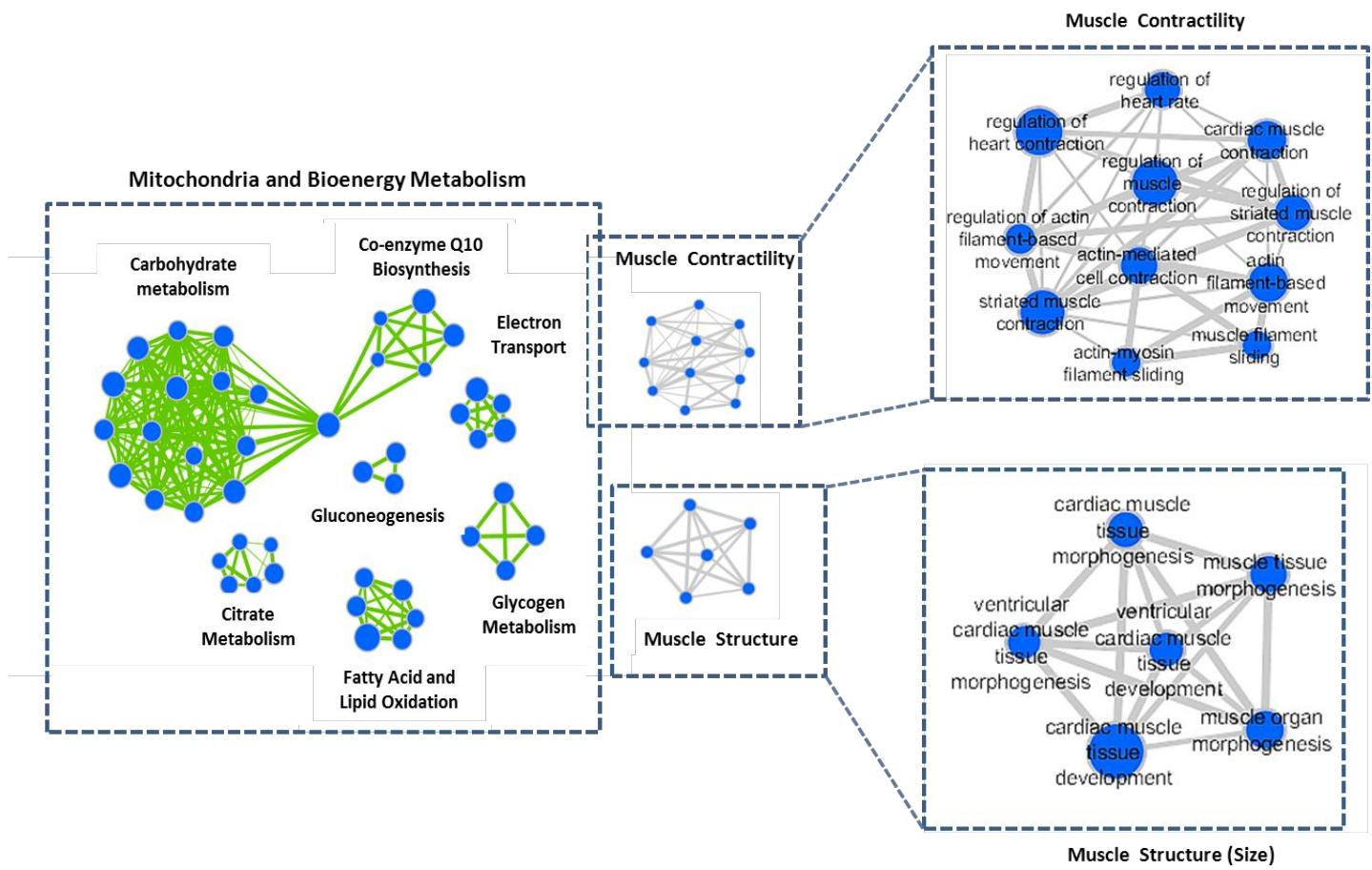
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## Module–trait relationships

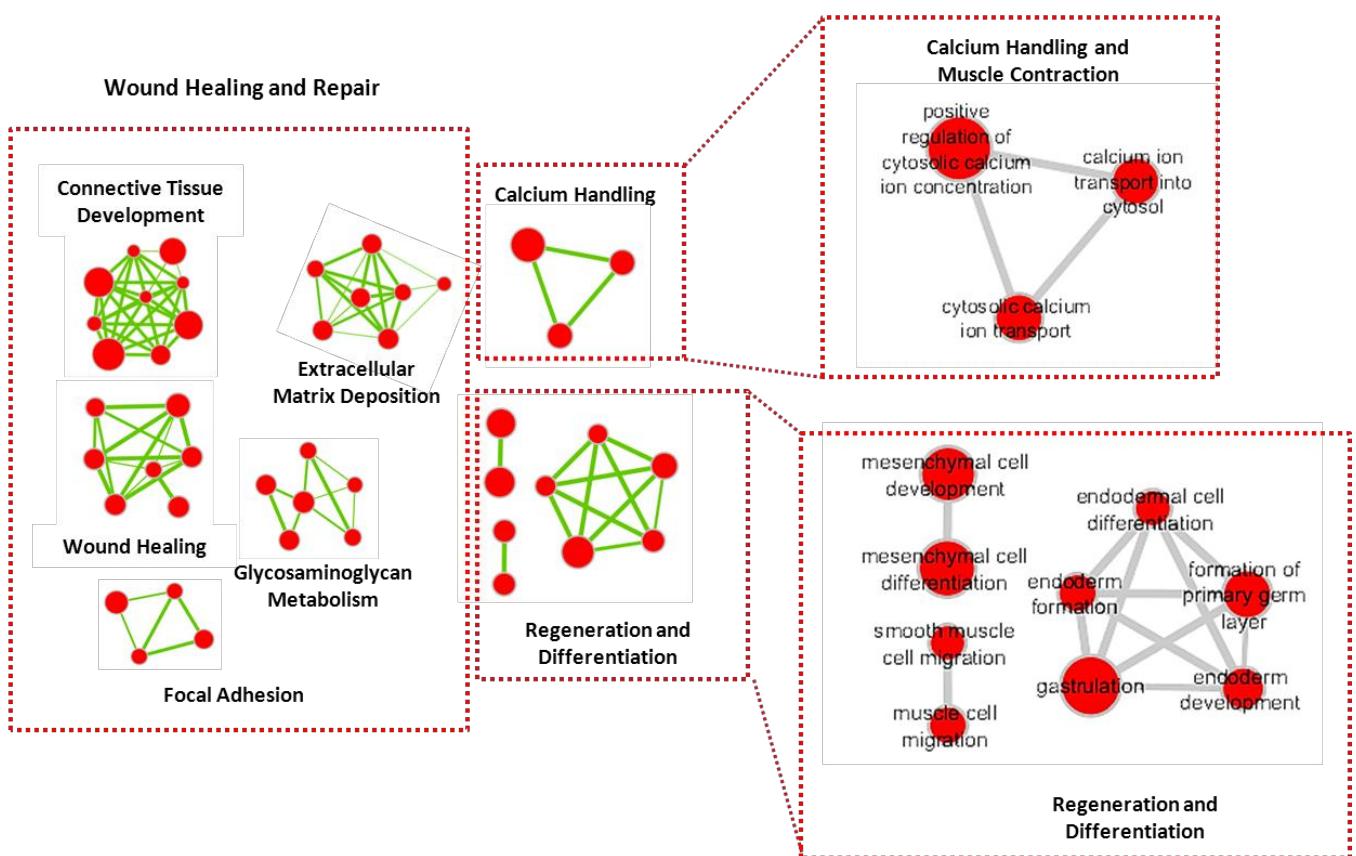


**a**

## Module 1 (Down-regulated Day 7 post ICU discharge)

**b**

## Module 3 (Up-regulated at Month 6 post-ICU discharge)



**Supplementary Table 1. Demographic and clinical differences for ICU acquired weakness patients (day 7 and month 6 post-ICU) and for healthy controls.**

Data are presented as Median and Interquartile range (IQR) unless specified

|   | Day 7<br>post ICU | Month 6<br>Post ICU | Control    | P-value# |
|---|-------------------|---------------------|------------|----------|
| Number of subjects  | 14                | 10                  | 8          |          |
| Age (mean [standard deviation])   | 50.3 (15.9)       | 48.1 (13.5)         | 35.3 (9.5) | 0.055    |
| Sex   | 7F 7M             | 5F 5M               | 3F 5M      | 1        |
| Quadriceps cross sectional area (percentage of age and sex matched norms) | 40.2 (24.1)       | 58.2 (31.2)         | 100*       | <0.001   |
| Quadriceps strength (%predicted isometric peak torque)                    | NA                | 67.9 (18.6)         | 100*       | <0.001   |
| FIM motor subscore (max score 91)   | 32 (27.5)         | 83 (6.0)            | 91*        | <0.001   |
| MRCSS (max score 60)  | 50 (5.0)          | 56 (4.5)            | 60*        | <0.001   |

\* Clinical data values for controls are set to the normal value in a healthy population

Abbreviations: Medical Research Council Sum Score (MRCSS). Functional Independence Measure (FIM). Female (F), Male (M). Data not available (NA).

#Differences between groups for non-normally distributed variables were tested using Kruskal-Wallis one-way analysis of variance. Differences between groups for normally distributed variables were tested using one-way ANOVA. Differences in categorical data (sex) between groups were tested using Fisher's exact test.

Supplementary Table 2: Differentially expressed genes (N = 744 unique probes corresponding to 695 genes). LIMMA global analysis of differentially expressed genes between ICUAW and controls for both day 7 post-ICU and month 6 post-ICU at false discovery rate (FDR) 5% level was performed using data adjusted for age, sex, and correlation between patient samples.

| Illumina ID  | HGNC      | Fold change             |                        | Fold change              |                        |
|--------------|-----------|-------------------------|------------------------|--------------------------|------------------------|
|              |           | ICUAW Day 7 vs. control | P value (FDR adjusted) | ICUAW Month 6 vs control | P value (FDR adjusted) |
| ILMN_1818859 | HS.407666 | -2.052                  | 2.51E-06               | -2.285                   | 3.86E-07               |
| ILMN_1710027 | PNMT      | 1.368                   | 0.00167                | 1.712                    | 2.38E-06               |
| ILMN_1883153 | HS.543175 | -1.707                  | 1.27E-05               | -1.748                   | 1.11E-05               |
| ILMN_1720745 | LOC645385 | 1.715                   | 1.15E-06               | 1.613                    | 1.43E-05               |
| ILMN_3245346 | EFR3B     | -1.874                  | 6.30E-07               | -1.703                   | 1.68E-05               |
| ILMN_1850374 | HS.333785 | -2.021                  | 5.77E-05               | -2.154                   | 2.75E-05               |
| ILMN_1903693 | HS.573359 | -1.684                  | 6.55E-05               | -1.77                    | 2.95E-05               |
| ILMN_1808825 | OR51F1    | -1.661                  | 0.000339               | -1.885                   | 3.00E-05               |
| ILMN_1897911 | HS.565086 | -2.101                  | 5.01E-05               | -2.182                   | 4.02E-05               |
| ILMN_1819158 | HS.542632 | -1.562                  | 0.00353                | -1.995                   | 4.29E-05               |
| ILMN_2283814 | C21ORF34  | -1.595                  | 0.000169               | -1.704                   | 4.72E-05               |
| ILMN_2157717 | MYF6      | -3.489                  | 0.000362               | -4.526                   | 5.22E-05               |
| ILMN_1893033 | HS.544451 | -1.936                  | 7.12E-05               | -2.01                    | 5.35E-05               |
| ILMN_1812461 | WISP2     | 1.302                   | 0.102                  | 2.115                    | 5.43E-05               |
| ILMN_1854165 | HS.564962 | -1.425                  | 0.000281               | -1.516                   | 5.66E-05               |
| ILMN_1817048 | HS.545044 | -1.922                  | 0.000337               | -2.172                   | 6.08E-05               |
| ILMN_1710458 | LOC646990 | -2.083                  | 0.000279               | -2.34                    | 6.80E-05               |
| ILMN_1822180 | HS.571435 | -1.596                  | 7.79E-05               | -1.62                    | 8.10E-05               |
| ILMN_1803882 | VEGFA     | -2.745                  | 1.51E-05               | -2.517                   | 8.52E-05               |
| ILMN_1716583 | NME7      | 1.783                   | 3.97E-05               | 1.758                    | 8.75E-05               |
| ILMN_1718766 | MT1F      | 1.624                   | 0.000812               | 1.828                    | 9.49E-05               |
| ILMN_2405023 | PPP1CB    | -1.424                  | 0.000483               | -1.517                   | 0.000102               |
| ILMN_1750763 | LOC643699 | -1.662                  | 0.000619               | -1.844                   | 0.000103               |
| ILMN_1728202 | TMEM22    | 1.348                   | 0.000661               | 1.595                    | 0.000109               |
| ILMN_1769229 | BCL2A1    | -1.438                  | 0.00159                | -1.608                   | 0.00012                |
| ILMN_1728787 | AGR3      | -1.696                  | 0.00027                | -1.791                   | 0.000124               |
| ILMN_2073235 | FTHL12    | -2.093                  | 1.08E-05               | -1.889                   | 0.000139               |
| ILMN_1889144 | HS.569953 | -1.762                  | 0.000689               | -1.959                   | 0.000143               |
| ILMN_1757081 | SYN2      | -1.635                  | 0.00142                | -1.872                   | 0.000144               |
| ILMN_1651429 | SELM      | 1.91                    | 0.000408               | 2.064                    | 0.00016                |
| ILMN_1732318 | PTK2B     | -1.684                  | 0.000323               | -1.769                   | 0.000163               |
| ILMN_1874302 | HS.543828 | -1.897                  | 0.000151               | -1.927                   | 0.00017                |
| ILMN_1838702 | HS.547858 | -1.564                  | 0.00303                | -1.842                   | 0.000174               |
| ILMN_1904242 | HS.114286 | -1.641                  | 0.000112               | -1.636                   | 0.000185               |
| ILMN_1703408 | FZD3      | 1.458                   | 0.000516               | 1.528                    | 0.000199               |
| ILMN_1687842 | PGA3      | -1.965                  | 0.000566               | -2.138                   | 0.000219               |
| ILMN_1699836 | LSP1      | -1.515                  | 0.000682               | -1.605                   | 0.000232               |
| ILMN_2181892 | BEX2      | 2.549                   | 0.00173                | 3.217                    | 0.000239               |
| ILMN_1914284 | HS.538083 | -1.931                  | 0.000341               | -2.011                   | 0.00025                |
| ILMN_1706660 | HYI       | 1.437                   | 0.000501               | 1.489                    | 0.000253               |
| ILMN_1659306 | SVIL      | -1.378                  | 0.00656                | -1.597                   | 0.000254               |
| ILMN_1854029 | HS.566801 | -1.775                  | 0.000419               | -1.858                   | 0.000256               |
| ILMN_1824465 | HS.148448 | -2.032                  | 8.32E-05               | -1.952                   | 0.000261               |
| ILMN_1780057 | RENBP     | 1.904                   | 0.000131               | 1.873                    | 0.000271               |
| ILMN_1778505 | LOC642771 | -2.101                  | 0.000581               | -2.269                   | 0.000284               |
| ILMN_1859160 | HS.117299 | -1.785                  | 0.000259               | -1.811                   | 0.000289               |
| ILMN_1877455 | HS.541892 | -1.763                  | 0.00203                | -2.031                   | 0.000289               |
| ILMN_1832180 | HS.557356 | -1.711                  | 0.000992               | -1.861                   | 0.000299               |
| ILMN_1720373 | SLC7A5    | -1.642                  | 0.00453                | -1.972                   | 0.000305               |
| ILMN_2128428 | DAB2      | 1.519                   | 0.0137                 | 1.946                    | 0.000324               |
| ILMN_2223941 | FBLN5     | 1.354                   | 0.00528                | 1.522                    | 0.000328               |
| ILMN_1777513 | KCTD11    | -1.345                  | 0.00464                | -1.497                   | 0.000331               |
| ILMN_3255124 | ATL1      | -1.627                  | 0.000678               | -1.709                   | 0.000341               |
| ILMN_1695058 | SLC38A5   | -1.83                   | 0.000104               | -1.762                   | 0.000343               |

|              |              |        |          |        |          |
|--------------|--------------|--------|----------|--------|----------|
| ILMN_1693270 | SUSD2        | 1.362  | 0.0257   | 1.725  | 0.000343 |
| ILMN_1874126 | HS.544721    | -1.41  | 0.0194   | -1.78  | 0.000344 |
| ILMN_1836172 | HS.582136    | -1.825 | 0.00216  | -2.106 | 0.00035  |
| ILMN_1832252 | HS.369978    | -1.631 | 0.000934 | -1.738 | 0.000364 |
| ILMN_1703233 | LOC653382    | -1.399 | 0.00358  | -1.55  | 0.000371 |
| ILMN_2132898 | SPRN         | -2.049 | 0.000181 | -2.008 | 0.000379 |
| ILMN_1706304 | EIF2C4       | -1.403 | 0.000618 | -1.442 | 0.000383 |
| ILMN_1705627 | USP2         | -1.734 | 0.000124 | -1.678 | 0.00039  |
| ILMN_1676361 | ARHGAP22     | 1.568  | 0.000745 | 1.638  | 0.000394 |
| ILMN_2358560 | TIAM2        | 1.534  | 0.0157   | 1.975  | 0.000418 |
| ILMN_1847029 | HS.553290    | -1.996 | 7.46E-05 | -1.859 | 0.00042  |
| ILMN_1668619 | KIAA1467     | 1.314  | 0.00317  | 1.416  | 0.000421 |
| ILMN_1772702 | SFRS2B       | 1.177  | 0.0558   | 1.395  | 0.000425 |
| ILMN_1807969 | SNCAP        | 1.295  | 0.0728   | 1.757  | 0.000438 |
| ILMN_1877156 | HS.567436    | -1.795 | 0.00112  | -1.939 | 0.000439 |
| ILMN_1888925 | HS.232535    | -1.63  | 0.000212 | -1.604 | 0.000459 |
| ILMN_1879135 | HS.555208    | -1.694 | 0.00236  | -1.894 | 0.000501 |
| ILMN_3274671 | LOC283481    | 1.754  | 1.70E-05 | 1.561  | 0.000519 |
| ILMN_1657009 | NFASC        | -1.546 | 0.00068  | -1.587 | 0.000524 |
| ILMN_1772369 | PDHA1        | -1.613 | 0.000347 | -1.608 | 0.00054  |
| ILMN_1813581 | CNR1         | 1.185  | 0.0951   | 1.478  | 0.000554 |
| ILMN_3203534 | LOC100132474 | -1.413 | 0.00367  | -1.547 | 0.000559 |
| ILMN_1861915 | HS.545663    | -1.244 | 0.0316   | -1.466 | 0.000565 |
| ILMN_1763730 | APPL1        | -1.657 | 4.54E-06 | -1.44  | 0.000569 |
| ILMN_2396991 | HCST         | 1.891  | 0.000189 | 1.818  | 0.000573 |
| ILMN_1711422 | PLEKHN1      | -1.555 | 0.00274  | -1.711 | 0.000574 |
| ILMN_1740217 | HACE1        | -1.553 | 0.000136 | -1.495 | 0.000575 |
| ILMN_1699357 | SLC22A5      | -1.772 | 0.00578  | -2.144 | 0.000578 |
| ILMN_2303955 | FKBP1B       | -1.53  | 0.00121  | -1.604 | 0.000581 |
| ILMN_2375879 | VEGFA        | -2.678 | 2.74E-05 | -2.219 | 0.00059  |
| ILMN_1663422 | RGL4         | -1.419 | 0.000363 | -1.413 | 0.000596 |
| ILMN_1692785 | KLHL21       | -1.385 | 0.0154   | -1.646 | 0.000616 |
| ILMN_2365686 | ALG8         | 1.789  | 6.23E-06 | 1.529  | 0.000619 |
| ILMN_1907597 | HS.553278    | -1.614 | 0.00362  | -1.818 | 0.000622 |
| ILMN_1833415 | LOC730877    | -1.517 | 0.00016  | -1.466 | 0.000633 |
| ILMN_2134538 | FTHL11       | -2.085 | 4.69E-05 | -1.846 | 0.000638 |
| ILMN_1902998 | HS.17661     | -1.472 | 0.00125  | -1.533 | 0.00064  |
| ILMN_1713918 | CYTH3        | -1.632 | 0.000979 | -1.696 | 0.000642 |
| ILMN_2392674 | PRR3         | -1.539 | 0.000622 | -1.56  | 0.000646 |
| ILMN_1663417 | C22ORF33     | -1.575 | 0.00332  | -1.748 | 0.000654 |
| ILMN_1713496 | ST3GAL5      | -1.425 | 0.00755  | -1.623 | 0.000655 |
| ILMN_1880885 | HS.545048    | -2.103 | 0.000443 | -2.097 | 0.000664 |
| ILMN_1819590 | HS.287720    | -1.62  | 0.000539 | -1.631 | 0.000669 |
| ILMN_1738207 | CISH         | -2.057 | 0.00918  | -2.731 | 0.000721 |
| ILMN_1914579 | HS.562118    | -1.447 | 0.00159  | -1.512 | 0.000731 |
| ILMN_1690780 | RFK          | -1.339 | 0.00719  | -1.48  | 0.000735 |
| ILMN_3178792 | HNRNPA2B1    | -1.391 | 0.000297 | -1.367 | 0.000764 |
| ILMN_1796126 | MXRA7        | -1.367 | 0.0091   | -1.541 | 0.000766 |
| ILMN_1666690 | ACRC         | -1.664 | 0.000392 | -1.64  | 0.00077  |
| ILMN_1807181 | BACH1        | -1.544 | 0.00416  | -1.716 | 0.000777 |
| ILMN_1674243 | TFRC         | -5.05  | 8.49E-08 | -2.485 | 0.000779 |
| ILMN_1823270 | HS.544326    | -1.485 | 0.00369  | -1.623 | 0.00078  |
| ILMN_1685433 | COL8A1       | 1.501  | 0.042    | 2.082  | 0.000785 |
| ILMN_1839905 | HS.544351    | -1.277 | 0.00807  | -1.392 | 0.000791 |
| ILMN_1860789 | HS.313056    | -2.035 | 0.000218 | -1.923 | 0.000799 |
| ILMN_2340643 | INSC         | -1.999 | 7.00E-04 | -2.029 | 0.000802 |
| ILMN_1791728 | SLC25A25     | -2.632 | 0.00101  | -2.778 | 0.000825 |
| ILMN_1859259 | HS.537451    | -1.569 | 0.00127  | -1.626 | 0.000838 |
| ILMN_1651967 | TP53I3       | -1.645 | 0.0044   | -1.855 | 0.000841 |
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| ILMN_1796663 | B4GALNT4     | 1.89   | 4.83E-05 | 1.676  | 0.000872 |
| ILMN_1670037 | POLR2L       | 1.351  | 0.0221   | 1.605  | 0.000876 |
| ILMN_1803813 | ASTE1        | 1.285  | 0.0409   | 1.56   | 0.000902 |
| ILMN_1776213 | RGMB         | -1.444 | 0.0125   | -1.689 | 0.000903 |
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| ILMN_1903750 | HS.544238    | -1.751 | 0.000183 | -1.651 | 0.000919 |
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| ILMN_2408885 | HDAC9        | -1.661 | 0.000101 | -1.541 | 0.000929 |
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| ILMN_1768534 | BHLHB2       | -1.802 | 0.0195   | -2.457 | 0.000953 |
| ILMN_2229877 | PCDH18       | 1.383  | 0.0322   | 1.721  | 0.000963 |
| ILMN_1816948 | HS.146561    | -1.418 | 0.00459  | -1.537 | 0.000976 |
| ILMN_1689142 | UBE1C        | -1.487 | 0.000575 | -1.476 | 0.000986 |
| ILMN_1736093 | SNX33        | 1.216  | 0.0326   | 1.388  | 0.000988 |
| ILMN_1821883 | HS.539119    | -1.788 | 0.00173  | -1.89  | 0.000993 |
| ILMN_1795336 | PTER         | -2.519 | 8.45E-06 | -1.928 | 0.001    |
| ILMN_1755843 | SLC26A8      | -1.407 | 0.00499  | -1.527 | 0.00101  |
| ILMN_3244456 | LOC100134122 | -1.46  | 0.0019   | -1.519 | 0.00102  |
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| ILMN_1703475 | LOC642981    | -1.712 | 0.000628 | -1.697 | 0.00105  |
| ILMN_1770787 | DDAH2        | 1.241  | 0.137    | 1.694  | 0.00105  |
| ILMN_1743836 | MXR47        | 1.111  | 0.35     | 1.512  | 0.00105  |
| ILMN_1653940 | USP2         | -1.451 | 0.00236  | -1.522 | 0.00106  |
| ILMN_1858507 | HS.544228    | -1.627 | 0.000919 | -1.642 | 0.00107  |
| ILMN_2400922 | OPRL1        | 1.283  | 0.00412  | 1.349  | 0.00108  |
| ILMN_1655296 | UTRN         | -1.939 | 0.0013   | -2.009 | 0.00109  |
| ILMN_1852279 | HS.528210    | -1.519 | 0.00102  | -1.536 | 0.00111  |
| ILMN_1719788 | LDHAL6B      | -1.574 | 0.00224  | -1.657 | 0.00112  |
| ILMN_2381603 | ING3         | 1.179  | 0.0682   | 1.38   | 0.00113  |
| ILMN_1850574 | HS.545111    | -1.518 | 0.00504  | -1.668 | 0.00115  |
| ILMN_1836060 | HS.582211    | -1.364 | 0.00575  | -1.472 | 0.00116  |
| ILMN_2220184 | GFP1         | 1.275  | 0.0162   | 1.422  | 0.00116  |
| ILMN_1909197 | HS.580452    | 1.273  | 0.0158   | 1.417  | 0.00116  |
| ILMN_1785191 | TMEM14A      | 1.431  | 0.0105   | 1.625  | 0.00116  |
| ILMN_1790985 | DJ341D10.1   | -1.393 | 0.0148   | -1.606 | 0.00117  |
| ILMN_2078074 | MUT          | -1.447 | 0.00467  | -1.564 | 0.00117  |
| ILMN_1670708 | F10          | 1.131  | 0.472    | 1.864  | 0.00117  |
| ILMN_1861128 | HS.543412    | -1.489 | 0.0185   | -1.802 | 0.00119  |
| ILMN_1738707 | S100A13      | 1.455  | 0.00899  | 1.641  | 0.00119  |
| ILMN_1792384 | HABP4        | 1.684  | 1.49E-05 | 1.458  | 0.0012   |
| ILMN_3241607 | LOC100132106 | -1.81  | 0.000175 | -1.671 | 0.00123  |
| ILMN_1879739 | HS.565146    | -1.34  | 0.0131   | -1.503 | 0.00123  |
| ILMN_1672662 | SLC20A1      | -1.518 | 0.00543  | -1.669 | 0.00123  |
| ILMN_2071809 | MGP          | 1.72   | 0.0213   | 2.269  | 0.00123  |
| ILMN_1909895 | HS.570330    | -1.218 | 0.118    | -1.563 | 0.00128  |
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| ILMN_1719641 | SMOC2        | 1.277  | 0.104    | 1.7    | 0.00129  |
| ILMN_1745005 | GGCT         | -1.509 | 2.12E-05 | -1.353 | 0.00132  |
| ILMN_1851912 | HS.385477    | -1.402 | 0.00263  | -1.457 | 0.00133  |
| ILMN_2085922 | WRB          | -1.455 | 0.000831 | -1.446 | 0.00137  |
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| ILMN_1882485 | HS.554595    | -1.458 | 6.89E-05 | -1.349 | 0.0014   |
| ILMN_1897230 | HS.543617    | -1.776 | 0.00346  | -1.926 | 0.00143  |
| ILMN_2088847 | OTUD5        | -1.25  | 0.0273   | -1.414 | 0.00144  |
| ILMN_1762106 | MMP2         | 1.468  | 0.00192  | 1.506  | 0.00145  |
| ILMN_3179396 | LOC100129410 | -1.493 | 0.00353  | -1.581 | 0.00146  |
| ILMN_1698334 | LOC728863    | -1.43  | 0.00156  | -1.451 | 0.00147  |
| ILMN_2344455 | G3BP1        | -1.242 | 0.0558   | -1.48  | 0.00149  |
| ILMN_1796431 | GPR101       | -1.807 | 0.00119  | -1.817 | 0.0015   |
| ILMN_1911873 | HS.544751    | -1.57  | 0.00217  | -1.626 | 0.0015   |

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| ILMN_3237099 | LOC100134815 | -1.605 | 0.000314 | -1.523 | 0.00152 |
| ILMN_1857546 | HS.575831    | -1.416 | 0.00272  | -1.467 | 0.00153 |
| ILMN_2252136 | YWHAE        | -1.198 | 0.0629   | -1.397 | 0.00156 |
| ILMN_1702489 | TRIM63       | -1.879 | 0.0038   | -2.056 | 0.00158 |
| ILMN_1706410 | HUS1B        | -1.693 | 0.00254  | -1.773 | 0.00162 |
| ILMN_1795464 | LTA          | -1.451 | 0.000859 | -1.434 | 0.00163 |
| ILMN_1817816 | HS.560319    | -1.406 | 0.0219   | -1.652 | 0.00164 |
| ILMN_2171783 | CPEB3        | -1.281 | 0.0637   | -1.579 | 0.00166 |
| ILMN_1860753 | HS.85445     | -1.529 | 0.000378 | -1.462 | 0.00168 |
| ILMN_1838836 | HS.282153    | -1.557 | 0.00182  | -1.587 | 0.00169 |
| ILMN_1658743 | CCNDBP1      | 1.65   | 4.16E-07 | 1.326  | 0.00172 |
| ILMN_1685483 | FETUB        | -1.934 | 3.89E-05 | -1.634 | 0.00173 |
| ILMN_1822220 | HS.128709    | -1.379 | 0.00409  | -1.443 | 0.00173 |
| ILMN_1734010 | C10ORF118    | 1.36   | 0.00577  | 1.443  | 0.00175 |
| ILMN_2327947 | SLC25A25     | -1.874 | 0.00394  | -2.041 | 0.00176 |
| ILMN_1728349 | TMEM63B      | -1.274 | 0.0126   | -1.382 | 0.00176 |
| ILMN_1703079 | NFS1         | -1.247 | 0.0284   | -1.403 | 0.00177 |
| ILMN_1703511 | PDZRN3       | -1.507 | 0.0273   | -1.867 | 0.00177 |
| ILMN_2277523 | DIP2A        | -1.5   | 0.00341  | -1.571 | 0.00178 |
| ILMN_1672331 | MAP3K7IP2    | -1.3   | 0.0102   | -1.402 | 0.0018  |
| ILMN_2189842 | SNORA10      | -1.164 | 0.225    | -1.54  | 0.0018  |
| ILMN_1781819 | PAPSS1       | 1.548  | 0.000211 | 1.445  | 0.00182 |
| ILMN_1691090 | MPV17        | 1.387  | 0.00427  | 1.453  | 0.00183 |
| ILMN_1799600 | STARD8       | -1.387 | 0.00347  | -1.438 | 0.00186 |
| ILMN_1675721 | UBE2R2       | -1.24  | 0.0125   | -1.329 | 0.00186 |
| ILMN_1889215 | HS.61208     | -1.947 | 0.00263  | -2.047 | 0.00187 |
| ILMN_2306565 | MTX2         | -1.3   | 0.00404  | -1.346 | 0.00187 |
| ILMN_2401730 | C1GALT1C1    | 1.689  | 1.96E-05 | 1.445  | 0.00188 |
| ILMN_1774207 | ANGPT2       | 2.043  | 0.000102 | 1.761  | 0.0019  |
| ILMN_1678116 | XAGE1E       | -1.455 | 0.00129  | -1.45  | 0.00192 |
| ILMN_1773125 | ENTPD1       | -1.999 | 0.000952 | -1.944 | 0.00195 |
| ILMN_1690802 | TRMT112      | 1.879  | 2.65E-06 | 1.475  | 0.00196 |
| ILMN_3230241 | LOC728975    | -1.657 | 0.0018   | -1.674 | 0.00204 |
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| ILMN_1696911 | FTHL8        | -1.955 | 8.01E-05 | -1.659 | 0.00245 |
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| ILMN_2053415 | LDLR         | -2.176 | 1.25E-05 | -1.67  | 0.00254 |
| ILMN_1671905 | C10ORF78     | 1.547  | 0.00161  | 1.535  | 0.00256 |
| ILMN_1748034 | KLHDC4       | 1.623  | 0.000153 | 1.463  | 0.00269 |
| ILMN_2174574 | HNRNPA3P1    | -1.956 | 2.42E-06 | -1.484 | 0.00282 |
| ILMN_1916513 | HS.572883    | -1.569 | 0.00166  | -1.549 | 0.0029  |
| ILMN_1781626 | C1S          | 1.697  | 0.000885 | 1.618  | 0.0029  |
| ILMN_2407389 | GPNMB        | 2.405  | 8.92E-06 | 1.744  | 0.00297 |
| ILMN_1859701 | HS.545514    | -1.634 | 0.000483 | -1.522 | 0.00301 |
| ILMN_1732410 | SLC16A9      | 2.371  | 0.000155 | 1.954  | 0.00304 |
| ILMN_1694466 | ZBED1        | -1.468 | 0.00166  | -1.449 | 0.00305 |
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| ILMN_1701386 | STRADB       | -1.845 | 1.31E-06 | -1.409 | 0.00315 |
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| ILMN_1715543 | ACOT1        | -1.584 | 0.000202 | -1.426 | 0.0038  |
| ILMN_1746948 | MYL5         | 4.574  | 0.00113  | 3.943  | 0.00385 |
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| ILMN_2345016 | PTGES2       | -1.418 | 0.000748 | -1.349 | 0.0042  |
| ILMN_1681754 | GGH          | 1.731  | 0.000878 | 1.608  | 0.00437 |
| ILMN_1667577 | LCMT2        | 1.44   | 0.000231 | 1.323  | 0.00438 |
| ILMN_1904843 | HS.129547    | -1.47  | 0.000709 | -1.386 | 0.00442 |
| ILMN_2173835 | FTHL3        | -1.795 | 0.000499 | -1.61  | 0.00465 |
| ILMN_1785891 | PRKD1        | 1.615  | 0.000934 | 1.514  | 0.00466 |
| ILMN_1654016 | MRLC2        | 1.519  | 2.55E-05 | 1.308  | 0.00467 |
| ILMN_2203588 | MYL5         | 4.935  | 0.00126  | 4.127  | 0.00476 |
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| ILMN_1870085 | HS.128892    | -1.688 | 0.00125  | -1.582 | 0.00524 |
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| ILMN_3250067 | ANGPT2       | 2.114  | 0.000572 | 1.834  | 0.00534 |
| ILMN_1704793 | MYPOP        | -1.616 | 4.79E-05 | -1.371 | 0.00557 |
| ILMN_2409167 | ANXA2        | 1.634  | 0.00187  | 1.558  | 0.0058  |
| ILMN_1884357 | HS.137293    | -1.692 | 0.00151  | -1.59  | 0.00582 |
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| ILMN_1742269 | LOC642726    | -1.681 | 0.00117  | -1.552 | 0.00644 |
| ILMN_2401258 | FAM13A       | 1.721  | 0.000162 | 1.467  | 0.00665 |
| ILMN_1849997 | HS.436627    | -1.681 | 0.0015   | -1.567 | 0.00671 |
| ILMN_1727618 | C8ORF38      | -1.434 | 0.000677 | -1.331 | 0.007   |
| ILMN_2358919 | TP53I3       | 2.14   | 0.000189 | 1.713  | 0.00714 |
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| ILMN_1890788 | HS.534997    | -1.522 | 0.00177  | -1.437 | 0.0078  |
| ILMN_1702247 | CCNDBP1      | 1.64   | 5.75E-06 | 1.309  | 0.0078  |
| ILMN_1651643 | ASB11        | -1.654 | 0.000224 | -1.428 | 0.00782 |
| ILMN_2215640 | TUBA3D       | -2.235 | 0.000316 | -1.794 | 0.00801 |
| ILMN_1805636 | PGAP3        | 1.491  | 0.00106  | 1.383  | 0.00812 |
| ILMN_1718961 | BNIIP3L      | 1.395  | 0.00089  | 1.303  | 0.00826 |
| ILMN_2403237 | CHN2         | 1.905  | 0.000264 | 1.582  | 0.0083  |
| ILMN_1774287 | CFB          | 1.707  | 0.00033  | 1.474  | 0.00831 |
| ILMN_1752510 | FAM13A       | 1.611  | 0.000418 | 1.424  | 0.00833 |
| ILMN_1892608 | HS.76704     | -1.482 | 0.00182  | -1.397 | 0.00887 |
| ILMN_1808792 | ALKBH6       | 1.438  | 0.000978 | 1.334  | 0.00906 |
| ILMN_2367275 | BCL7B        | -1.401 | 0.000524 | -1.286 | 0.0091  |
| ILMN_3247023 | FLJ22536     | 1.716  | 0.000583 | 1.503  | 0.0091  |
| ILMN_1735822 | TTC30A       | 1.651  | 7.14E-05 | 1.372  | 0.00925 |
| ILMN_1806601 | GRSF1        | -1.437 | 9.70E-05 | -1.263 | 0.00931 |
| ILMN_1782167 | RPL32        | 1.448  | 8.86E-05 | 1.267  | 0.00941 |
| ILMN_1801348 | GOT2         | -2.048 | 4.84E-06 | -1.455 | 0.00955 |
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| ILMN_3233388 | RELL1        | -1.512 | 0.000357 | -1.341 | 0.0102  |
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| ILMN_1703335 | LACTB        | -1.488 | 0.00044  | -1.331 | 0.0105  |
| ILMN_1814924 | FAM55C       | -1.691 | 0.000261 | -1.433 | 0.0107  |
| ILMN_1828245 | HS.542149    | -1.485 | 0.000946 | -1.357 | 0.0107  |
| ILMN_2336647 | NNT          | -1.802 | 2.97E-05 | -1.407 | 0.0107  |
| ILMN_1712754 | NFKBIB       | -1.441 | 0.000955 | -1.322 | 0.0114  |
| ILMN_2104877 | CMPK1        | -1.342 | 0.0014   | -1.264 | 0.0115  |
| ILMN_1811754 | NDUFB10      | -1.566 | 6.51E-06 | -1.262 | 0.0115  |
| ILMN_2153485 | NMNMAT3      | -1.737 | 9.45E-05 | -1.412 | 0.0115  |

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| ILMN_2336133 | SULT1A4      | 1.423  | 0.000623 | 1.295  | 0.0115 |
| ILMN_1754244 | MYH8         | 12.6   | 0.000134 | 5.056  | 0.0117 |
| ILMN_1712530 | AKAP1        | -1.612 | 0.000649 | -1.419 | 0.0118 |
| ILMN_1807359 | CLEC11A      | 1.568  | 0.00191  | 1.444  | 0.0118 |
| ILMN_1741180 | HEXDC        | -1.455 | 0.00107  | -1.334 | 0.0119 |
| ILMN_1704369 | LIMA1        | 1.576  | 0.00115  | 1.422  | 0.0119 |
| ILMN_1690085 | STK11IP      | 1.389  | 0.000533 | 1.266  | 0.0119 |
| ILMN_1752199 | LHPP         | 1.377  | 0.000601 | 1.261  | 0.0122 |
| ILMN_3247835 | CXORF64      | 1.695  | 0.00122  | 1.505  | 0.0124 |
| ILMN_1763941 | LRRK49       | 1.413  | 0.000546 | 1.279  | 0.0126 |
| ILMN_1745152 | UQCC         | -1.434 | 0.00059  | -1.295 | 0.0127 |
| ILMN_3182171 | FGGY         | 1.931  | 0.000504 | 1.593  | 0.0127 |
| ILMN_2307656 | AGTRAP       | 2.38   | 2.86E-05 | 1.629  | 0.0128 |
| ILMN_2368773 | FAM3C        | 1.443  | 0.000578 | 1.3    | 0.0128 |
| ILMN_1796244 | CD2BP2       | 1.682  | 2.01E-06 | 1.278  | 0.0132 |
| ILMN_1764043 | TTL          | -1.566 | 0.0016   | -1.424 | 0.0133 |
| ILMN_1718853 | UQCRC2       | -1.381 | 0.000522 | -1.255 | 0.0135 |
| ILMN_1790891 | CKAP4        | 1.424  | 0.00139  | 1.313  | 0.014  |
| ILMN_1729130 | C7ORF42      | 1.547  | 0.000196 | 1.323  | 0.0141 |
| ILMN_1739496 | PRRX1        | 1.552  | 0.00191  | 1.415  | 0.0148 |
| ILMN_2183784 | TTC12        | 1.593  | 0.000782 | 1.397  | 0.015  |
| ILMN_1745779 | TCTEX1D2     | 1.532  | 0.000279 | 1.321  | 0.0151 |
| ILMN_1748077 | DDX59        | -1.57  | 0.000465 | -1.36  | 0.0152 |
| ILMN_1795839 | SCCPDH       | -1.522 | 0.00146  | -1.378 | 0.0152 |
| ILMN_1801205 | GPNMB        | 2.524  | 2.09E-05 | 1.642  | 0.0152 |
| ILMN_2326512 | CASP1        | 1.685  | 0.000186 | 1.389  | 0.0153 |
| ILMN_2305225 | NDRG4        | -1.761 | 9.03E-05 | -1.399 | 0.0155 |
| ILMN_1796773 | BTBD8        | -2.057 | 4.10E-05 | -1.496 | 0.0156 |
| ILMN_1802089 | SYMPK        | 1.547  | 0.000453 | 1.344  | 0.0157 |
| ILMN_1724266 | LYPD2        | -1.422 | 0.000643 | -1.279 | 0.0159 |
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| ILMN_1708516 | PRTFDC1      | 1.408  | 0.00136  | 1.293  | 0.0162 |
| ILMN_1858599 | HS.20255     | 1.487  | 0.0012   | 1.341  | 0.0163 |
| ILMN_1767816 | APH1B        | 1.451  | 0.000728 | 1.299  | 0.0165 |
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| ILMN_1723834 | FLJ32011     | -1.456 | 0.00155  | -1.326 | 0.0176 |
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| ILMN_1703370 | ZDHHC12      | 1.554  | 9.72E-05 | 1.288  | 0.0194 |
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| ILMN_1724533 | LY96         | 2.094  | 0.000848 | 1.667  | 0.0197 |
| ILMN_1682993 | NKG7         | 2.604  | 0.000161 | 1.765  | 0.0202 |
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| ILMN_1729509 | C1ORF43      | -1.41  | 0.000164 | -1.225 | 0.021  |
| ILMN_2397880 | CSTF3        | 1.422  | 0.00151  | 1.291  | 0.021  |

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| ILMN_1775182 | GSR          | -1.5   | 0.000832 | -1.317 | 0.0215 |
| ILMN_1663605 | RNF123       | -1.324 | 0.00128  | -1.22  | 0.0219 |
| ILMN_1704477 | COX5A        | -1.387 | 0.000172 | -1.212 | 0.0223 |
| ILMN_1838863 | HS.497591    | -1.602 | 0.000941 | -1.38  | 0.0223 |
| ILMN_1761309 | ADCK5        | 1.488  | 0.000221 | 1.269  | 0.0224 |
| ILMN_2048607 | ANKRD9       | -1.414 | 0.000979 | -1.268 | 0.0226 |
| ILMN_3244650 | FLJ41941     | -3.582 | 0.000157 | -2.098 | 0.0227 |
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| ILMN_1815882 | HNRNPA1      | 1.512  | 0.000606 | 1.305  | 0.0244 |
| ILMN_1707475 | UBE2E2       | 1.458  | 0.000289 | 1.255  | 0.0245 |
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| ILMN_2128967 | C11ORF1      | 1.851  | 8.60E-05 | 1.396  | 0.0254 |
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| ILMN_1749403 | TSPAN33      | -1.484 | 0.001    | -1.303 | 0.0256 |
| ILMN_1791388 | ZNF787       | -1.457 | 0.00067  | -1.273 | 0.0264 |
| ILMN_2367428 | FAM96A       | -1.825 | 0.000281 | -1.428 | 0.0266 |
| ILMN_1731233 | GZMH         | 2.274  | 0.00053  | 1.671  | 0.027  |
| ILMN_1739886 | HNF4A        | -2.04  | 0.00012  | -1.48  | 0.0271 |
| ILMN_1788099 | LSM4         | 1.372  | 0.00171  | 1.247  | 0.0276 |
| ILMN_1741475 | C7ORF47      | 1.576  | 0.000164 | 1.291  | 0.0277 |
| ILMN_2156172 | HK2          | -1.892 | 0.000458 | -1.477 | 0.028  |
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| ILMN_2360291 | UGCGL1       | 1.46   | 0.000571 | 1.266  | 0.0283 |
| ILMN_1704398 | FZD9         | -1.673 | 0.0013   | -1.414 | 0.0287 |
| ILMN_1701998 | AFAP1        | 1.673  | 0.00186  | 1.434  | 0.0288 |
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| ILMN_2334296 | IL18BP       | 1.75   | 0.000322 | 1.388  | 0.0296 |
| ILMN_1714861 | CD68         | 2.134  | 0.00178  | 1.686  | 0.0303 |
| ILMN_1710756 | ENO1         | 1.465  | 0.000271 | 1.245  | 0.0305 |
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| ILMN_2094166 | CHMP5        | 1.57   | 0.000126 | 1.274  | 0.0314 |
| ILMN_1660602 | C10RF43      | -1.411 | 0.000597 | -1.235 | 0.0315 |
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| ILMN_1778478 | CCDC28B      | -1.758 | 0.00077  | -1.415 | 0.0348 |
| ILMN_2180315 | ATG4D        | -1.381 | 0.000655 | -1.216 | 0.0349 |
| ILMN_1751206 | MLLT10       | -2.194 | 0.000208 | -1.536 | 0.035  |
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| ILMN_1731699 | RAB15        | 1.998  | 0.00109  | 1.549  | 0.0358 |
| ILMN_1902571 | HS.557622    | -1.696 | 0.000169 | -1.323 | 0.0374 |

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| ILMN_1722309 | ENDOG     | -1.829 | 3.53E-05 | -1.327 | 0.038  |
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| ILMN_1736940 | HPRT1     | 1.668  | 4.07E-05 | 1.273  | 0.039  |
| ILMN_1767129 | ABCC8     | 1.796  | 0.00028  | 1.376  | 0.0399 |
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| ILMN_1703005 | IFP38     | -1.413 | 0.00127  | -1.241 | 0.0408 |
| ILMN_1683576 | MAGED2    | 1.669  | 0.00101  | 1.367  | 0.0408 |
| ILMN_1787344 | LOC652078 | -1.374 | 0.00134  | -1.221 | 0.0411 |
| ILMN_3307930 | RAN       | 1.379  | 0.000327 | 1.192  | 0.0416 |
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| ILMN_1718852 | PLCL1     | -1.616 | 0.0016   | -1.353 | 0.0443 |
| ILMN_1748916 | C18ORF55  | -1.625 | 0.000122 | -1.273 | 0.0445 |
| ILMN_1698307 | DBNL      | 1.578  | 0.000295 | 1.276  | 0.0445 |
| ILMN_1786612 | PSME2     | 1.573  | 0.000101 | 1.248  | 0.0447 |
| ILMN_1798485 | ATP6V1E1  | 1.438  | 0.00104  | 1.242  | 0.0459 |
| ILMN_2345319 | PREPL     | 1.694  | 0.000369 | 1.33   | 0.0459 |
| ILMN_2244841 | ALDH4A1   | 1.836  | 0.000539 | 1.405  | 0.046  |
| ILMN_1779616 | SUCLG1    | -1.54  | 7.09E-05 | -1.226 | 0.0465 |
| ILMN_1787109 | CLK2      | 1.397  | 0.00116  | 1.222  | 0.0473 |
| ILMN_1764266 | CKMT2     | -1.948 | 0.00011  | -1.383 | 0.0476 |
| ILMN_1666306 | SRRD      | -1.534 | 0.00032  | -1.255 | 0.0476 |
| ILMN_1673026 | CHCHD3    | -1.6   | 0.000167 | -1.266 | 0.0477 |
| ILMN_2376502 | RHOBTB1   | -1.668 | 0.0019   | -1.38  | 0.0479 |
| ILMN_1652357 | PDHX      | -1.454 | 0.00133  | -1.254 | 0.049  |
| ILMN_1759023 | WFS1      | 1.422  | 0.00131  | 1.236  | 0.0496 |
| ILMN_1700349 | ADCK4     | 1.513  | 0.000316 | 1.243  | 0.0497 |
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| ILMN_1812777 | MRPL35    | -1.423 | 0.000583 | -1.215 | 0.0503 |
| ILMN_1772261 | GLG1      | 1.587  | 0.000141 | 1.254  | 0.0503 |
| ILMN_1722622 | CD163     | 1.968  | 0.00191  | 1.524  | 0.0507 |
| ILMN_3247821 | TMEM206   | 1.44   | 0.000372 | 1.213  | 0.0507 |
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| ILMN_1695717 | RBM41     | -1.412 | 0.000855 | -1.215 | 0.0544 |
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| ILMN_1758827 | RTN4IP1   | -1.63  | 0.000295 | -1.282 | 0.0557 |
| ILMN_1692896 | JMJD4     | 1.476  | 0.000878 | 1.243  | 0.0564 |
| ILMN_1745271 | EXOSC4    | 1.628  | 0.00152  | 1.334  | 0.0568 |
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| ILMN_2109708 | ECGF1     | 1.746  | 0.000583 | 1.349  | 0.0569 |
| ILMN_1733690 | AKAP7     | -1.985 | 0.000661 | -1.451 | 0.0572 |
| ILMN_1715508 | NNMT      | 6.627  | 0.00039  | 2.657  | 0.0574 |
| ILMN_1665123 | NMNAT3    | -1.57  | 0.00166  | -1.308 | 0.0575 |
| ILMN_2138801 | TP73L     | 1.94   | 0.000216 | 1.384  | 0.0575 |
| ILMN_2342695 | PDGFA     | -1.591 | 0.000809 | -1.293 | 0.0577 |
| ILMN_1786278 | FAM149A   | -2.402 | 0.000124 | -1.506 | 0.0583 |
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| ILMN_1663532 | RIC8B     | -1.601 | 7.24E-05 | -1.234 | 0.0589 |
| ILMN_2355665 | MTP18     | -2.38  | 0.00159  | -1.664 | 0.0594 |
| ILMN_1652006 | SMC1A     | 1.405  | 0.000493 | 1.195  | 0.0594 |
| ILMN_1774272 | ESRRA     | -1.62  | 0.000154 | -1.256 | 0.0598 |
| ILMN_1652906 | GBTGT1    | 1.324  | 0.00145  | 1.176  | 0.0611 |
| ILMN_1740633 | PRF1      | 1.556  | 0.000997 | 1.276  | 0.0627 |
| ILMN_1700081 | FST       | 5.63   | 0.000403 | 2.401  | 0.0628 |

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| ILMN_2406892 | C19ORF2      | -1.463 | 0.00015  | -1.194 | 0.0631 |
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| ILMN_1741599 | MEMO1        | -1.448 | 0.000466 | -1.207 | 0.0648 |
| ILMN_1689828 | DMPK         | 2.21   | 0.000285 | 1.47   | 0.0658 |
| ILMN_1656186 | SLC41A1      | -1.944 | 0.000185 | -1.365 | 0.066  |
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| ILMN_2345739 | CAPRIN2      | 1.99   | 1.16E-05 | 1.3    | 0.0666 |
| ILMN_1712067 | CCDC135      | -1.413 | 0.00168  | -1.219 | 0.067  |
| ILMN_1741148 | ALDOA        | -1.613 | 7.43E-05 | -1.23  | 0.0673 |
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| ILMN_3253126 | FLJ41484     | 3.161  | 0.000127 | 1.676  | 0.0693 |
| ILMN_1752728 | FUCA1        | 1.75   | 0.000267 | 1.305  | 0.0695 |
| ILMN_1738866 | DEXI         | -1.558 | 0.000231 | -1.23  | 0.0716 |
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| ILMN_1705397 | PDK2         | -1.851 | 0.000481 | -1.356 | 0.0734 |
| ILMN_1669409 | VSIG4        | 1.619  | 0.00189  | 1.314  | 0.0734 |
| ILMN_2393341 | LIAS         | -1.632 | 0.00017  | -1.247 | 0.074  |
| ILMN_1765746 | SFT2D3       | 1.476  | 0.00117  | 1.233  | 0.0741 |
| ILMN_1813344 | C20ORF7      | -1.507 | 0.00102  | -1.242 | 0.0751 |
| ILMN_1810228 | TTF2         | 2.499  | 5.86E-05 | 1.459  | 0.076  |
| ILMN_2099586 | CCDC28B      | -1.717 | 0.00162  | -1.347 | 0.0765 |
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| ILMN_3246608 | CENPV        | -1.745 | 0.00143  | -1.352 | 0.0781 |
| ILMN_1703324 | PDSS1        | -1.62  | 0.000177 | -1.24  | 0.0781 |
| ILMN_1681503 | MCM2         | 1.689  | 0.000179 | 1.263  | 0.0784 |
| ILMN_1761084 | FNDC5        | -2.019 | 0.00103  | -1.443 | 0.0785 |
| ILMN_1810875 | SYNGR1       | -1.684 | 0.000264 | -1.271 | 0.0785 |
| ILMN_1655694 | LOC642031    | -1.58  | 0.000173 | -1.224 | 0.0801 |
| ILMN_1801045 | SPIN3        | 1.349  | 0.00125  | 1.172  | 0.0805 |
| ILMN_2350607 | C20ORF7      | -1.555 | 0.00168  | -1.272 | 0.0807 |
| ILMN_1672081 | NEURL        | -1.718 | 0.00175  | -1.342 | 0.0827 |
| ILMN_1814823 | FTL          | 1.637  | 0.000998 | 1.287  | 0.0837 |
| ILMN_3193306 | C14ORF109    | -1.446 | 0.000419 | -1.189 | 0.0846 |
| ILMN_2409055 | FAM13C1      | 2.061  | 0.000791 | 1.432  | 0.0856 |
| ILMN_1772964 | CCL8         | 1.881  | 0.000796 | 1.367  | 0.0869 |
| ILMN_1794230 | SCAND1       | 1.442  | 0.00175  | 1.217  | 0.0872 |
| ILMN_1779324 | GZMA         | 2.003  | 0.00113  | 1.427  | 0.0875 |
| ILMN_2052331 | MYOC         | -2.382 | 0.000656 | -1.523 | 0.0876 |
| ILMN_2219556 | ISCA1        | -1.485 | 0.000971 | -1.217 | 0.0911 |
| ILMN_1785892 | MASP1        | -3.601 | 6.55E-07 | -1.456 | 0.0928 |
| ILMN_1731851 | OXA1L        | -1.445 | 0.000205 | -1.171 | 0.0933 |
| ILMN_1806349 | SLC6A8       | -1.76  | 1.65E-05 | -1.222 | 0.0951 |
| ILMN_3237286 | LOC100132794 | -2.261 | 5.73E-05 | -1.369 | 0.0957 |
| ILMN_1713985 | MAF1         | -1.347 | 0.000603 | -1.149 | 0.0974 |
| ILMN_2405305 | ARNTL        | 2.342  | 0.000809 | 1.503  | 0.0977 |
| ILMN_1662640 | C20ORF127    | 2.355  | 0.000735 | 1.501  | 0.0979 |
| ILMN_3271630 | FGGY         | 1.772  | 0.000284 | 1.282  | 0.0987 |
| ILMN_1653466 | HES4         | -1.891 | 0.000797 | -1.354 | 0.0991 |
| ILMN_1747759 | WSB1         | 1.433  | 0.00125  | 1.195  | 0.101  |
| ILMN_1712430 | ATP5G1       | -2.616 | 0.00189  | -1.643 | 0.102  |
| ILMN_1745368 | TMEM50A      | 1.501  | 0.000934 | 1.215  | 0.102  |
| ILMN_1667079 | SPTBN2       | -2.028 | 0.000155 | -1.334 | 0.103  |
| ILMN_1804328 | WWP1         | -1.542 | 0.000456 | -1.213 | 0.104  |
| ILMN_2080637 | ZBTB44       | -1.497 | 0.00164  | -1.226 | 0.104  |
| ILMN_1787526 | MGC13057     | -1.916 | 0.000397 | -1.33  | 0.105  |
| ILMN_2355042 | CLUAP1       | 1.342  | 0.000919 | 1.15   | 0.105  |
| ILMN_3225941 | LOC728368    | 1.527  | 0.00132  | 1.231  | 0.105  |
| ILMN_1755462 | UGCG1        | 1.562  | 7.20E-05 | 1.185  | 0.106  |
| ILMN_1735495 | TBC1D8       | -1.717 | 0.00144  | -1.305 | 0.108  |
| ILMN_1779040 | INO80B       | 1.651  | 0.000612 | 1.254  | 0.108  |

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| ILMN_1783681 | MRPL34        | -1.509 | 0.0017   | -1.226 | 0.111 |
| ILMN_2329927 | ABCG1         | 2.271  | 0.00074  | 1.45   | 0.113 |
| ILMN_2412927 | GMPPB         | 1.569  | 0.000731 | 1.226  | 0.113 |
| ILMN_1801504 | RUNX1         | 3.376  | 0.000189 | 1.626  | 0.115 |
| ILMN_1761981 | FAM96A        | -1.763 | 5.11E-05 | -1.225 | 0.117 |
| ILMN_1777129 | C16ORF56      | 1.393  | 0.000767 | 1.161  | 0.117 |
| ILMN_1771957 | MAN1B1        | 1.412  | 0.00161  | 1.182  | 0.117 |
| ILMN_1903345 | HS.575085     | -1.375 | 0.000641 | -1.151 | 0.119 |
| ILMN_2049021 | PTTG3P        | 1.933  | 0.000826 | 1.346  | 0.119 |
| ILMN_2073289 | MTSS1         | 1.81   | 7.75E-05 | 1.244  | 0.12  |
| ILMN_1700047 | ALAS1         | -1.793 | 0.000204 | -1.259 | 0.121 |
| ILMN_1798712 | USP4          | -1.337 | 0.000795 | -1.139 | 0.121 |
| ILMN_1654690 | CECR5         | -1.564 | 0.000236 | -1.195 | 0.122 |
| ILMN_1721669 | IDH3B         | -1.848 | 3.60E-05 | -1.236 | 0.122 |
| ILMN_1737604 | FLJ10986      | 1.964  | 0.000962 | 1.358  | 0.122 |
| ILMN_1719468 | EPM2A         | -1.382 | 0.00163  | -1.167 | 0.123 |
| ILMN_2377669 | CD247         | 1.851  | 0.000993 | 1.322  | 0.123 |
| ILMN_1769520 | UBE2L6        | 1.624  | 0.00021  | 1.208  | 0.127 |
| ILMN_2261416 | CD3D          | 1.652  | 0.00148  | 1.263  | 0.129 |
| ILMN_1803856 | DKFZP586I1420 | 1.669  | 0.000821 | 1.251  | 0.129 |
| ILMN_1790549 | TSPAN3        | 1.509  | 0.000475 | 1.187  | 0.129 |
| ILMN_1802458 | AGTRAP        | 1.856  | 0.000698 | 1.305  | 0.13  |
| ILMN_1698934 | CMTM7         | 2.819  | 0.000392 | 1.525  | 0.13  |
| ILMN_1801553 | LEO1          | 1.487  | 0.00131  | 1.199  | 0.131 |
| ILMN_2412564 | NCBP2         | 1.608  | 0.000218 | 1.201  | 0.131 |
| ILMN_1716264 | ANKRD1        | 2.477  | 0.000674 | 1.472  | 0.132 |
| ILMN_3235065 | ZNHIT6        | 1.321  | 0.00152  | 1.137  | 0.132 |
| ILMN_1656951 | APCDD1        | -1.676 | 0.00116  | -1.26  | 0.133 |
| ILMN_1799488 | ZNF383        | -1.459 | 0.000758 | -1.176 | 0.133 |
| ILMN_2175114 | KCNS3         | -1.913 | 0.0014   | -1.344 | 0.134 |
| ILMN_1871457 | HS.534680     | 2.17   | 0.000151 | 1.334  | 0.134 |
| ILMN_1712678 | RPS27L        | 1.722  | 0.000192 | 1.229  | 0.134 |
| ILMN_1687519 | SNAP23        | 1.533  | 0.000665 | 1.198  | 0.135 |
| ILMN_1784447 | PLCE1         | 2.779  | 0.000267 | 1.487  | 0.136 |
| ILMN_2383383 | PIR           | 1.547  | 0.00068  | 1.202  | 0.137 |
| ILMN_1739847 | EIF3D         | 1.423  | 0.000473 | 1.153  | 0.139 |
| ILMN_1660900 | SNORA7B       | 1.475  | 0.00153  | 1.191  | 0.144 |
| ILMN_1740429 | FTL           | 1.615  | 0.0014   | 1.234  | 0.149 |
| ILMN_2324561 | SLC7A6        | 2.577  | 0.000237 | 1.42   | 0.15  |
| ILMN_2111739 | MAN2C1        | 1.771  | 5.62E-05 | 1.207  | 0.151 |
| ILMN_1737124 | PRPF4B        | 1.391  | 0.0017   | 1.157  | 0.153 |
| ILMN_2042771 | PTTG1         | 2.058  | 0.000433 | 1.322  | 0.154 |
| ILMN_1784186 | C1ORF170      | -2.591 | 0.000166 | -1.398 | 0.159 |
| ILMN_1675617 | NT5M          | -1.461 | 0.00132  | -1.175 | 0.16  |
| ILMN_3194432 | LOC100129913  | 1.667  | 0.000882 | 1.231  | 0.161 |
| ILMN_2412822 | SCN3B         | 1.907  | 0.000358 | 1.272  | 0.162 |
| ILMN_1751431 | WIBG          | 1.446  | 0.000431 | 1.15   | 0.162 |
| ILMN_1721337 | MRPS18B       | -1.443 | 0.000639 | -1.154 | 0.164 |
| ILMN_1755047 | LRRK2         | -2.388 | 0.00156  | -1.45  | 0.165 |
| ILMN_3200830 | LOC649553     | 1.503  | 0.000437 | 1.166  | 0.165 |
| ILMN_1795826 | ATP6V0D1      | 1.402  | 0.00055  | 1.138  | 0.166 |
| ILMN_1775111 | SND1          | 1.397  | 0.000961 | 1.145  | 0.167 |
| ILMN_1780188 | B3GALNT2      | -1.393 | 0.00123  | -1.147 | 0.168 |
| ILMN_1814917 | TLE2          | -1.812 | 0.000399 | -1.246 | 0.168 |
| ILMN_1652806 | ATP5J         | -1.639 | 0.00109  | -1.223 | 0.169 |
| ILMN_3243961 | ZNF252        | -1.537 | 0.0017   | -1.2   | 0.172 |
| ILMN_1711729 | LOC442454     | -1.302 | 0.00152  | -1.116 | 0.176 |
| ILMN_1728355 | PSMD4         | 1.448  | 0.000751 | 1.153  | 0.176 |
| ILMN_1815115 | CYC1          | -1.364 | 0.000742 | -1.127 | 0.177 |
| ILMN_2136971 | FABP3         | -2.558 | 0.000109 | -1.358 | 0.177 |
| ILMN_3305304 | POLD2         | 1.351  | 0.000731 | 1.122  | 0.178 |

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| ILMN_1788053 | SLC25A12  | -1.773 | 0.00019  | -1.214 | 0.18  |
| ILMN_1770479 | LMO7      | 1.703  | 0.000255 | 1.203  | 0.18  |
| ILMN_1787879 | ARL2      | 1.362  | 0.000212 | 1.111  | 0.181 |
| ILMN_1799024 | VAC14     | 1.501  | 0.000558 | 1.163  | 0.181 |
| ILMN_1653129 | CSTF2     | 1.39   | 0.00169  | 1.146  | 0.182 |
| ILMN_2070072 | RPS7      | 2.046  | 0.000175 | 1.27   | 0.183 |
| ILMN_1805161 | LZTR1     | 1.364  | 0.00186  | 1.137  | 0.186 |
| ILMN_1760741 | NDUFA9    | -1.573 | 0.00124  | -1.194 | 0.191 |
| ILMN_1699071 | C21ORF7   | 2.565  | 0.000491 | 1.401  | 0.191 |
| ILMN_2326509 | CASP1     | 1.72   | 0.000251 | 1.199  | 0.195 |
| ILMN_1734867 | NR2C1     | 1.493  | 0.000661 | 1.156  | 0.198 |
| ILMN_1800096 | MPST      | -1.542 | 0.000263 | -1.154 | 0.202 |
| ILMN_2199926 | OR7E37P   | -2.67  | 0.000317 | -1.391 | 0.202 |
| ILMN_1705224 | TMEM110   | -1.972 | 0.000118 | -1.289 | 0.209 |
| ILMN_2384591 | HN1       | 2.223  | 9.67E-07 | 1.193  | 0.21  |
| ILMN_1786308 | NIPSNAP3B | -2.243 | 0.000208 | -1.292 | 0.211 |
| ILMN_1777444 | STX5      | 1.44   | 0.00129  | 1.147  | 0.211 |
| ILMN_1672024 | ISCA1L    | -1.597 | 0.00112  | -1.188 | 0.212 |
| ILMN_1758034 | ETFDH     | -1.71  | 0.000477 | -1.2   | 0.214 |
| ILMN_2214098 | BIVM      | -1.442 | 0.00165  | -1.149 | 0.217 |
| ILMN_3239284 | B9D1      | 1.519  | 0.00176  | 1.174  | 0.217 |
| ILMN_1705297 | MYBPH     | 7.733  | 0.00129  | 2.096  | 0.228 |
| ILMN_1807610 | PRPH2     | 1.83   | 0.000658 | 1.226  | 0.23  |
| ILMN_1815107 | MATR3     | 1.443  | 0.000826 | 1.134  | 0.232 |
| ILMN_3306482 | LOC730107 | -1.486 | 0.00191  | -1.159 | 0.233 |
| ILMN_2228732 | CCNG2     | 2.393  | 0.00139  | 1.366  | 0.236 |
| ILMN_1748836 | FUZ       | -1.375 | 0.00123  | -1.119 | 0.237 |
| ILMN_2358733 | TAZ       | -1.361 | 0.0016   | -1.118 | 0.239 |
| ILMN_1731418 | SP110     | 1.491  | 0.000875 | 1.143  | 0.244 |
| ILMN_1680501 | GTF2IRD2B | -2.077 | 0.000164 | -1.234 | 0.246 |
| ILMN_1786444 | LPL       | -2.103 | 0.00182  | -1.307 | 0.246 |
| ILMN_1665132 | CD36      | -3.09  | 4.31E-05 | -1.335 | 0.253 |
| ILMN_1669709 | TMEM108   | -1.788 | 6.00E-04 | -1.202 | 0.255 |
| ILMN_1750722 | RPS7      | 1.731  | 0.00187  | 1.215  | 0.255 |
| ILMN_1671442 | WDR43     | 1.358  | 0.00166  | 1.113  | 0.257 |
| ILMN_1662917 | LMO1      | -2.117 | 0.00124  | -1.288 | 0.259 |
| ILMN_1696087 | PHB2      | -1.335 | 0.000933 | -1.099 | 0.261 |
| ILMN_2405521 | MTHFD2    | 2.771  | 3.76E-05 | 1.289  | 0.261 |
| ILMN_2306189 | MAGED1    | 1.726  | 0.000325 | 1.175  | 0.262 |
| ILMN_1656368 | ALDH4A1   | 1.441  | 0.00183  | 1.135  | 0.263 |
| ILMN_2091310 | TMEM16A   | -1.425 | 0.000562 | -1.115 | 0.264 |
| ILMN_2201533 | C17ORF61  | 1.437  | 0.000415 | 1.115  | 0.264 |
| ILMN_2234873 | NME2      | -1.671 | 0.00109  | -1.182 | 0.269 |
| ILMN_1783333 | C16ORF61  | -1.607 | 0.00175  | -1.174 | 0.273 |
| ILMN_2358457 | ATF4      | -1.547 | 0.00147  | -1.155 | 0.278 |
| ILMN_2240866 | MASP1     | -4.5   | 3.58E-06 | -1.364 | 0.278 |
| ILMN_1814022 | NR1H3     | 1.581  | 0.000407 | 1.141  | 0.281 |
| ILMN_1655311 | LOC145853 | -2.029 | 5.16E-06 | -1.159 | 0.283 |
| ILMN_2185563 | ANKRA2    | 1.664  | 0.000159 | 1.144  | 0.286 |
| ILMN_1722239 | TIMM8A    | -1.689 | 0.0015   | -1.185 | 0.287 |
| ILMN_1814726 | SCARB2    | 1.416  | 0.000231 | 1.098  | 0.29  |
| ILMN_2262288 | EEF1G     | -1.431 | 0.0011   | -1.117 | 0.295 |
| ILMN_1736077 | LIAS      | -1.553 | 0.00178  | -1.153 | 0.296 |
| ILMN_1672382 | SLC38A3   | -2.083 | 0.000109 | -1.202 | 0.296 |
| ILMN_2399893 | RPS24     | 1.591  | 0.0014   | 1.157  | 0.298 |
| ILMN_1687533 | SEMA4D    | 1.843  | 0.000718 | 1.195  | 0.301 |
| ILMN_2373632 | IDH3B     | -1.926 | 0.000497 | -1.201 | 0.305 |
| ILMN_1808501 | SH3KBP1   | -2.289 | 0.00107  | -1.283 | 0.305 |
| ILMN_1814589 | LOC728037 | -1.818 | 0.000525 | -1.181 | 0.309 |
| ILMN_1806634 | NNT       | -1.599 | 0.00104  | -1.147 | 0.319 |
| ILMN_1652797 | FAM174B   | 3.098  | 0.000116 | 1.312  | 0.319 |

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| ILMN_1784365 | MYOG      | 2.486  | 0.000449 | 1.277  | 0.32  |
| ILMN_1733176 | LIMS1     | -1.457 | 0.000603 | -1.108 | 0.324 |
| ILMN_1691364 | STAT1     | 1.753  | 0.000319 | 1.155  | 0.326 |
| ILMN_1780698 | ZFYVE19   | -1.356 | 0.00122  | -1.093 | 0.328 |
| ILMN_1686664 | MT2A      | 3.595  | 0.000754 | 1.418  | 0.335 |
| ILMN_2361768 | CHRNA1    | 7.065  | 7.50E-05 | 1.549  | 0.336 |
| ILMN_1676980 | MTSS1     | 1.608  | 0.000442 | 1.129  | 0.342 |
| ILMN_2043918 | DLEU1     | -1.787 | 0.000382 | -1.157 | 0.345 |
| ILMN_1722855 | VEGFB     | -1.825 | 2.18E-05 | -1.127 | 0.35  |
| ILMN_1766000 | PM20D2    | 1.607  | 0.00158  | 1.144  | 0.354 |
| ILMN_1740430 | SLC2A4RG  | -1.366 | 0.00185  | -1.093 | 0.358 |
| ILMN_1680072 | ZNF32     | -1.442 | 0.000354 | -1.092 | 0.36  |
| ILMN_1810782 | SH3KBP1   | -2.279 | 0.000792 | -1.238 | 0.362 |
| ILMN_1723494 | SIRT2     | -1.425 | 0.00166  | -1.102 | 0.369 |
| ILMN_1775522 | MAGED1    | 1.659  | 0.000851 | 1.138  | 0.371 |
| ILMN_3239735 | WASH5P    | 1.439  | 0.000469 | 1.092  | 0.371 |
| ILMN_1798700 | CHRNA1    | 6.066  | 0.000113 | 1.471  | 0.372 |
| ILMN_2304512 | SAA1      | 15.44  | 5.02E-05 | 1.733  | 0.373 |
| ILMN_1893633 | LOC439949 | -1.617 | 0.00125  | -1.136 | 0.374 |
| ILMN_1804662 | NRG4      | -2.055 | 0.000237 | -1.177 | 0.375 |
| ILMN_1779751 | C7ORF55   | -1.537 | 0.00122  | -1.118 | 0.381 |
| ILMN_1743205 | ABCA7     | 1.656  | 0.00105  | 1.135  | 0.391 |
| ILMN_2052208 | GADD45A   | 3.921  | 0.000458 | 1.372  | 0.391 |
| ILMN_1671402 | ARPP-21   | 2.802  | 9.00E-04 | 1.289  | 0.392 |
| ILMN_1694111 | PNKP      | 1.392  | 0.000647 | 1.082  | 0.395 |
| ILMN_2376289 | DBNL      | 1.72   | 0.000667 | 1.137  | 0.396 |
| ILMN_1768101 | HOXB6     | -1.742 | 0.000327 | -1.122 | 0.427 |
| ILMN_1786189 | MKI67IP   | 1.437  | 0.00159  | 1.089  | 0.44  |
| ILMN_2400661 | ZNF626    | 1.479  | 0.000394 | 1.083  | 0.441 |
| ILMN_1686906 | TP53INP2  | -2.245 | 0.000789 | -1.192 | 0.443 |
| ILMN_1727740 | SYNCRIP   | 1.451  | 0.0017   | 1.091  | 0.445 |
| ILMN_1722206 | MAF       | 1.576  | 0.00145  | 1.109  | 0.449 |
| ILMN_1690754 | SVIL      | 1.682  | 0.000353 | 1.109  | 0.452 |
| ILMN_1758315 | SLC9A9    | 1.753  | 0.000369 | 1.117  | 0.454 |
| ILMN_3197097 | TSTD1     | 2.163  | 0.00137  | 1.182  | 0.47  |
| ILMN_2148668 | RCBTB2    | 1.721  | 0.00052  | 1.111  | 0.476 |
| ILMN_1672161 | ARPP-21   | 1.983  | 1.03E-05 | 1.103  | 0.478 |
| ILMN_1780298 | FAM86A    | 1.864  | 0.00071  | 1.131  | 0.48  |
| ILMN_1704446 | SLC6A10P  | -1.599 | 0.000127 | -1.082 | 0.486 |
| ILMN_1652505 | APEX2     | 1.663  | 0.00183  | 1.115  | 0.49  |
| ILMN_1694075 | GADD45A   | 2.897  | 0.000864 | 1.224  | 0.507 |
| ILMN_1814315 | PBXIP1    | 1.617  | 3.62E-05 | 1.07   | 0.521 |
| ILMN_1798827 | SRBD1     | 1.313  | 0.00189  | -1.055 | 0.528 |
| ILMN_3269324 | FLJ37644  | -2.205 | 0.000361 | -1.139 | 0.531 |
| ILMN_1701514 | TRAF3IP2  | 1.78   | 0.000785 | 1.107  | 0.535 |
| ILMN_1699695 | TNFRSF21  | 1.825  | 0.00158  | 1.116  | 0.547 |
| ILMN_1765409 | STAM      | 1.341  | 0.00184  | -1.056 | 0.549 |
| ILMN_3234884 | KIF22     | -1.829 | 0.00108  | -1.108 | 0.562 |
| ILMN_1775703 | TRAPPC6A  | 1.486  | 0.00125  | 1.069  | 0.568 |
| ILMN_1897333 | HS.18849  | 1.522  | 0.000264 | 1.062  | 0.575 |
| ILMN_1726981 | VEGFB     | -1.737 | 0.00017  | -1.078 | 0.581 |
| ILMN_2119224 | KIFAP3    | 1.457  | 0.000561 | 1.059  | 0.581 |
| ILMN_1682147 | HOOK2     | -1.803 | 0.000348 | -1.089 | 0.582 |
| ILMN_1751803 | LSM10     | -1.539 | 0.00174  | -1.075 | 0.586 |
| ILMN_1728047 | AKR1A1    | 1.912  | 0.000245 | 1.093  | 0.588 |
| ILMN_1676197 | LRP11     | 1.454  | 0.00129  | 1.062  | 0.589 |
| ILMN_1658110 | C18ORF19  | -1.506 | 0.000271 | -1.057 | 0.596 |
| ILMN_1662886 | KLHL34    | -2.945 | 0.000323 | -1.157 | 0.605 |
| ILMN_2044832 | NOP56     | 1.368  | 0.00127  | 1.046  | 0.631 |
| ILMN_1887174 | KIAA0146  | 1.362  | 0.00183  | 1.044  | 0.652 |
| ILMN_1737344 | DDX41     | 1.337  | 0.00111  | 1.039  | 0.654 |

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| ILMN_1696601 | VARS     | 1.581  | 0.00188  | 1.06   | 0.683 |
| ILMN_1674706 | MTHFD2   | 2.349  | 0.00045  | 1.096  | 0.688 |
| ILMN_1671478 | CKB      | -4.343 | 2.12E-05 | -1.132 | 0.689 |
| ILMN_1704380 | INCA1    | -1.469 | 0.00116  | -1.045 | 0.697 |
| ILMN_1690105 | STAT1    | 1.705  | 0.000891 | 1.059  | 0.709 |
| ILMN_1742358 | CA14     | -2.773 | 0.00189  | -1.11  | 0.74  |
| ILMN_1678191 | GDF10    | -1.658 | 6.50E-05 | -1.038 | 0.75  |
| ILMN_2289825 | ARPP-21  | 1.866  | 1.41E-05 | 1.04   | 0.758 |
| ILMN_1869087 | HS.40289 | 1.502  | 0.000566 | 1.033  | 0.768 |
| ILMN_1798181 | IRF7     | 2.177  | 0.000341 | 1.054  | 0.798 |
| ILMN_1673409 | MGC16121 | 7.084  | 2.13E-07 | 1.074  | 0.82  |
| ILMN_1674629 | C9ORF3   | -1.916 | 0.000138 | -1.034 | 0.832 |
| ILMN_1762093 | ABCC12   | -3.1   | 0.000168 | -1.056 | 0.845 |
| ILMN_1800008 | ACAT1    | -1.53  | 0.00144  | -1.025 | 0.845 |
| ILMN_2212763 | ICAM3    | -1.666 | 0.000394 | -1.024 | 0.862 |
| ILMN_1698673 | EFCAB7   | 3.54   | 0.00031  | 1.056  | 0.867 |
| ILMN_1730523 | FAM195A  | -1.697 | 0.000468 | -1.019 | 0.895 |
| ILMN_1764596 | MPST     | -1.558 | 3.00E-04 | -1.005 | 0.964 |
| ILMN_2380771 | AKR1A1   | 1.684  | 0.00156  | 1      | 0.999 |

**Supplementary Table 3: Enrichment analysis of 347 differentially expressed genes** (downregulated in ICUAW post-ICU day 7 vs controls) at FDR adjusted P-value < 0.05. Gene Ontology (GO) or Human Phenotype (HP) terms with FDR adjusted P-value (hypergeometric test) < 0.05.

| Gene Ontology (GO) or<br>Human Phenotype (HP) term | Description   | FDR adjusted P-value<br>(hypergeometric test) |
|--|---|---|
| GO:0044429   | mitochondrial part                                    | 2.02E-14                                      |
| GO:0005743   | mitochondrial inner membrane                          | 8.50E-11                                      |
| GO:0045333   | cellular respiration                                  | 9.35E-10                                      |
| GO:0051186   | cofactor metabolic process                            | 0.00494                                       |
| HP:0001941   | Acidosis  | 0.0129  |
| GO:0019752   | carboxylic acid metabolic process                     | 0.0134  |
| GO:0035383   | thioester metabolic process                           | 0.0137  |
| GO:0001954   | positive regulation of cell-matrix adhesion           | 0.0141  |
| GO:0045244   | succinate-CoA ligase complex (GDP-forming)            | 0.0381  |
| GO:0043183   | vascular endothelial growth factor receptor 1 binding | 0.0381  |
| GO:0004776   | succinate-CoA ligase (GDP-forming) activity           | 0.0381  |
| GO:0006082   | organic acid metabolic process                        | 0.0492  |

Please note that **Supplementary table 4** is only available as an Excel file.

**Supplementary Table 5: Association of module eigengene values with disease status.**

Differences in ME expression were tested using a linear mixed effects model to account for correlation between patient samples: ICUAW day 7 vs control and ICUAW month 6 vs control.

| Module | Coefficient<br>ICUAW Day 7 vs.<br>control | FDR Adjusted<br>P-Value | Coefficient<br>ICUAW Month 6 vs.<br>control | FDR Adjusted P-Value |
|--------|---|-------------------------|---|----------------------|
| 1      | -2.604E-01                                | 5.770E-05               | -9.307E-02                                  | 1.791E-01            |
| 2      | 3.067E-01                                 | 2.820E-08               | 9.377E-02                                   | 1.127E-01            |
| 3      | 3.983E-02                                 | 5.990E-01               | 1.757E-01                                   | 2.805E-02            |
| 4      | -2.638E-01                                | 3.340E-05               | -9.430E-02                                  | 1.641E-01            |
| 5      | 5.260E-02                                 | 5.118E-01               | -4.590E-02                                  | 5.920E-01            |
| 6      | 1.906E-01                                 | 1.032E-02               | 1.159E-01                                   | 1.435E-01            |
| 7      | 1.836E-01                                 | 1.236E-02               | 5.736E-02                                   | 4.627E-01            |
| 8      | 1.397E-01                                 | 7.228E-02               | 5.585E-02                                   | 5.019E-01            |
| 9      | -2.380E-02                                | 7.718E-01               | -2.675E-02                                  | 7.606E-01            |
| 10     | 1.249E-01                                 | 9.043E-02               | -5.129E-02                                  | 5.156E-01            |
| 11     | 1.736E-01                                 | 1.994E-02               | 1.755E-01                                   | 2.589E-02            |
| 12     | 2.446E-01                                 | 2.450E-04               | 9.116E-02                                   | 1.955E-01            |
| 13     | 2.092E-01                                 | 3.922E-03               | 1.325E-01                                   | 8.747E-02            |
| 14     | 1.923E-01                                 | 3.689E-03               | -2.564E-02                                  | 7.157E-01            |
| 15     | 8.912E-02                                 | 2.361E-01               | -6.525E-02                                  | 4.152E-01            |
| 16     | -2.312E-01                                | 4.178E-04               | -2.067E-01                                  | 2.636E-03            |
| 17     | -2.067E-01                                | 3.918E-03               | -7.180E-02                                  | 3.491E-01            |

**Supplementary Table 6a. Module 1 Functional Enrichment.** Gene Ontology and Human Phenotype categories with FDR < 0.05

| Gene Ontology (GO) or Human Phenotype (HP) term | Description   | FDR adjusted P-value (hypergeometric test) |
|---|---|--|
| GO:0006091                                      | generation of precursor metabolites and energy        | 2.71E-22                                   |
| GO:0015980                                      | energy derivation by oxidation of organic compounds   | 2.56E-18                                   |
| GO:0030016                                      | myofibril   | 4.69E-15                                   |
| GO:0044429                                      | mitochondrial part                                    | 5.23E-14                                   |
| GO:0003012                                      | muscle system process                                 | 9.62E-13                                   |
| HP:0003198                                      | Myopathy  | 1.34E-10                                   |
| GO:0005743                                      | mitochondrial inner membrane                          | 2.78E-10                                   |
| GO:0006006                                      | glucose metabolic process                             | 1.43E-09                                   |
| GO:0019752                                      | carboxylic acid metabolic process                     | 7.65E-09                                   |
| GO:0060048                                      | cardiac muscle contraction                            | 8.50E-09                                   |
| GO:0008307                                      | structural constituent of muscle                      | 9.59E-09                                   |
| GO:0070252                                      | actin-mediated cell contraction                       | 1.08E-08                                   |
| GO:0006733                                      | oxidoreduction coenzyme metabolic process             | 1.40E-08                                   |
| GO:0009167                                      | purine ribonucleoside monophosphate metabolic process | 1.62E-08                                   |
| GO:0048037                                      | cofactor binding                                      | 3.11E-08                                   |
| HP:0001941                                      | Acidosis  | 8.29E-08                                   |
| GO:1990204                                      | oxidoreductase complex                                | 1.11E-07                                   |
| GO:0046128                                      | purine ribonucleoside metabolic process               | 1.69E-07                                   |
| GO:0070469                                      | respiratory chain                                     | 6.68E-06                                   |
| GO:0061061                                      | muscle structure development                          | 8.54E-06                                   |
| GO:0044712                                      | single-organism catabolic process                     | 1.16E-05                                   |
| HP:0001644                                      | Dilated cardiomyopathy                                | 1.21E-05                                   |
| GO:0046496                                      | nicotinamide nucleotide metabolic process             | 1.49E-05                                   |
| GO:0042383                                      | sarcolemma  | 3.32E-05                                   |
| GO:0016491                                      | oxidoreductase activity                               | 3.88E-05                                   |
| HP:0002605                                      | Hepatic necrosis                                      | 5.77E-05                                   |
| GO:0019395                                      | fatty acid oxidation                                  | 8.65E-05                                   |
| HP:0003674                                      | Onset   | 8.68E-05                                   |
| HP:0011021                                      | Abnormality of circulating enzyme level               | 0.000114                                   |
| HP:0004354                                      | Abnormality of carboxylic acid metabolism             | 0.000131                                   |
| GO:0006811                                      | ion transport   | 0.000165                                   |
| GO:0055008                                      | cardiac muscle tissue morphogenesis                   | 0.000328                                   |
| HP:0011675                                      | Arrhythmia  | 0.000374                                   |
| GO:0042578                                      | phosphoric ester hydrolase activity                   | 0.000448                                   |
| GO:0016311                                      | dephosphorylation                                     | 0.000456                                   |
| HP:0011804                                      | Abnormality of muscle physiology                      | 0.000494                                   |
| GO:0055085                                      | transmembrane transport                               | 0.000503                                   |
| GO:0006744                                      | ubiquinone biosynthetic process                       | 0.000544                                   |
| GO:0006942                                      | regulation of striated muscle contraction             | 0.000834                                   |
| GO:0022892                                      | substrate-specific transporter activity               | 0.00118                                    |
| HP:0001635                                      | Congestive heart failure                              | 0.0012                                     |
| GO:0048878                                      | chemical homeostasis                                  | 0.00149                                    |
| HP:0002171                                      | Gliosis   | 0.00179                                    |
| GO:0009055                                      | electron carrier activity                             | 0.0022                                     |
| HP:0001992                                      | Organic aciduria                                      | 0.00228                                    |
| GO:0055010                                      | ventricular cardiac muscle tissue morphogenesis       | 0.00266                                    |
| HP:0001943                                      | Hypoglycemia  | 0.00276                                    |
| GO:0014850                                      | response to muscle activity                           | 0.00302                                    |
| GO:0042805                                      | actinin binding                                       | 0.00327                                    |
| GO:0016459                                      | myosin complex  | 0.00347                                    |
| HP:0012103                                      | Abnormality of the mitochondrion                      | 0.00386                                    |
| GO:0006749                                      | glutathione metabolic process                         | 0.00445                                    |
| HP:0100578                                      | Lipoatrophy   | 0.00476                                    |
| HP:0001325                                      | Hypoglycemic coma                                     | 0.00639                                    |
| HP:0001711                                      | Abnormality of the left ventricle                     | 0.00658                                    |
| GO:0072709                                      | cellular response to sorbitol                         | 0.00687                                    |
| GO:0055100                                      | adiponectin binding                                   | 0.00687                                    |
| GO:0031444                                      | slow-twitch skeletal muscle fiber contraction         | 0.00687                                    |
| GO:0000309                                      | nicotinamide-nucleotide adenylyltransferase activity  | 0.00687                                    |
| GO:0009081                                      | branched-chain amino acid metabolic process           | 0.00705                                    |
| GO:0086001                                      | cardiac muscle cell action potential                  | 0.00896                                    |

|            |   |        |
|------------|---|--------|
| GO:0016769 | transferase activity, transferring nitrogenous groups                     | 0.0106 |
| GO:0070069 | cytochrome complex  | 0.014  |
| HP:0000982 | Palmoplantar keratoderma  | 0.0199 |
| HP:0001714 | Ventricular hypertrophy   | 0.0224 |
| GO:0046323 | glucose import  | 0.0226 |
| HP:0003691 | Scapular winging  | 0.0236 |
| GO:0004619 | phosphoglycerate mutase activity  | 0.0262 |
| GO:0004515 | nicotinate-nucleotide adenylyltransferase activity                        | 0.0262 |
| GO:0004083 | bisphosphoglycerate 2-phosphatase activity                                | 0.0262 |
| GO:0004082 | bisphosphoglycerate mutase activity                                       | 0.0262 |
| HP:0012438 | Abnormal gallbladder physiology   | 0.027  |
| GO:1901700 | response to oxygen-containing compound                                    | 0.0315 |
| GO:0016765 | transferase activity, transferring alkyl or aryl (other than methyl) grou | 0.0348 |
| HP:0000602 | Ophthalmoplegia   | 0.0351 |
| HP:0100022 | Abnormality of movement   | 0.0366 |
| GO:0042803 | protein homodimerization activity   | 0.0369 |
| HP:0002018 | Nausea  | 0.0463 |
| GO:0005516 | calmodulin binding  | 0.0463 |

**Supplementary Table 6b. Module 2 Functional Enrichment.** Gene Ontology and Human Phenotype categories with the highest enrichment.

| Gene Ontology (GO) or Human Phenotype (HP) term | Description                                   | FDR adjusted P-value (hypergeometric test) |
|---|---|--|
| GO:0044822                                      | poly(A) RNA binding                           | 3.94E-23                                   |
| GO:0005730                                      | nucleolus                                     | 3.48E-17                                   |
| GO:0042254                                      | ribosome biogenesis                           | 9.62E-13                                   |
| GO:0034660                                      | ncRNA metabolic process                       | 7.22E-09                                   |
| GO:0030529                                      | ribonucleoprotein complex                     | 1.79E-07                                   |
| GO:0044419                                      | interspecies interaction between organisms    | 3.34E-07                                   |
| GO:0016032                                      | viral process                                 | 4.04E-07                                   |
| GO:0033365                                      | protein localization to organelle             | 5.02E-07                                   |
| GO:0006401                                      | RNA catabolic process                         | 2.34E-06                                   |
| GO:0000956                                      | nuclear-transcribed mRNA catabolic process    | 2.34E-06                                   |
| GO:0019083                                      | viral transcription                           | 8.48E-06                                   |
| GO:0006886                                      | intracellular protein transport               | 1.15E-05                                   |
| GO:0006612                                      | protein targeting to membrane                 | 3.01E-05                                   |
| GO:0045047                                      | protein targeting to ER                       | 3.31E-05                                   |
| GO:0044445                                      | cytosolic part                                | 4.40E-05                                   |
| GO:0042623                                      | ATPase activity, coupled                      | 0.00029                                    |
| GO:0006412                                      | translation                                   | 0.0015                                     |
| GO:0000783                                      | nuclear telomere cap complex                  | 0.00172                                    |
| GO:0048770                                      | pigment granule                               | 0.00187                                    |
| GO:0010888                                      | negative regulation of lipid storage          | 0.0024                                     |
| GO:0046688                                      | response to copper ion                        | 0.004                                      |
| GO:0009113                                      | purine nucleobase biosynthetic process        | 0.00706                                    |
| GO:0033256                                      | I-kappaB/NF-kappaB complex                    | 0.00878                                    |
| GO:0030515                                      | snoRNA binding                                | 0.00882                                    |
| GO:0010875                                      | positive regulation of cholesterol efflux     | 0.0124                                     |
| GO:0010745                                      | negative regulation of macrophage derived     | 0.0124                                     |
| HP:0002015                                      | Dysphagia                                     | 0.014                                      |
| GO:2000113                                      | negative regulation of cellular macromolecule | 0.0163                                     |
| GO:0005774                                      | vacuolar membrane                             | 0.0185                                     |
| GO:0071294                                      | cellular response to zinc ion                 | 0.0202                                     |
| GO:0071345                                      | cellular response to cytokine stimulus        | 0.026                                      |
| HP:0003749                                      | Pelvic girdle muscle weakness                 | 0.027                                      |
| HP:0003547                                      | Shoulder girdle muscle weakness               | 0.027                                      |
| GO:0006974                                      | cellular response to DNA damage stimulus      | 0.0276                                     |
| GO:0010501                                      | RNA secondary structure unwinding             | 0.0297                                     |
| GO:0000049                                      | tRNA binding                                  | 0.0297                                     |
| GO:0071276                                      | cellular response to cadmium ion              | 0.0313                                     |
| GO:0042162                                      | telomeric DNA binding                         | 0.0313                                     |
| GO:0032204                                      | regulation of telomere maintenance            | 0.0313                                     |
| GO:0003735                                      | structural constituent of ribosome            | 0.0343                                     |
| GO:0010629                                      | negative regulation of gene expression        | 0.0347                                     |
| HP:0004377                                      | Hematological neoplasm                        | 0.0404                                     |
| GO:0045323                                      | interleukin-1 receptor complex                | 0.0443                                     |
| GO:0038027                                      | apolipoprotein A-I-mediated signaling pathway | 0.0443                                     |
| GO:0006177                                      | GMP biosynthetic process                      | 0.0443                                     |
| GO:0015949                                      | nucleobase-containing small molecule          | 0.0465                                     |
| HP:0001288                                      | Gait disturbance                              | 0.05                                       |

**Supplementary Table 6c. Module 3 Functional Enrichment.** Gene Ontology and Human Phenotype categories with FDR < 0.05

| Gene Ontology (GO) or Human Phenotype (HP) term | Description   | FDR adjusted P-value<br>(hypergeometric test) |
|---|---|---|
| GO:0005578                                      | proteinaceous extracellular matrix                      | 1.67E-33                                      |
| GO:0043062                                      | extracellular structure organization                    | 1.36E-32                                      |
| GO:0005615                                      | extracellular space                                     | 1.85E-31                                      |
| GO:0022610                                      | biological adhesion                                     | 8.68E-20                                      |
| GO:0070161                                      | anchoring junction                                      | 2.00E-19                                      |
| GO:0005509                                      | calcium ion binding                                     | 1.40E-18                                      |
| GO:0042060                                      | wound healing   | 1.66E-17                                      |
| GO:2000145                                      | regulation of cell motility                             | 2.64E-16                                      |
| GO:0007596                                      | blood coagulation                                       | 7.52E-15                                      |
| GO:0001568                                      | blood vessel development                                | 9.05E-15                                      |
| GO:0032963                                      | collagen metabolic process                              | 1.20E-14                                      |
| GO:0032403                                      | protein complex binding                                 | 3.27E-14                                      |
| GO:0031252                                      | cell leading edge                                       | 7.50E-14                                      |
| GO:0005581                                      | collagen trimer   | 4.52E-13                                      |
| GO:0050839                                      | cell adhesion molecule binding                          | 5.40E-13                                      |
| GO:0005178                                      | integrin binding  | 6.90E-13                                      |
| GO:0000904                                      | cell morphogenesis involved in differentiation          | 3.52E-12                                      |
| GO:0022617                                      | extracellular matrix disassembly                        | 3.54E-12                                      |
| GO:0005539                                      | glycosaminoglycan binding                               | 6.84E-12                                      |
| GO:0007167                                      | enzyme linked receptor protein signaling pathway        | 1.57E-11                                      |
| GO:0030574                                      | collagen catabolic process                              | 2.20E-11                                      |
| GO:0005201                                      | extracellular matrix structural constituent             | 3.15E-11                                      |
| GO:0015629                                      | actin cytoskeleton                                      | 6.64E-11                                      |
| GO:0009986                                      | cell surface  | 1.16E-10                                      |
| GO:0030036                                      | actin cytoskeleton organization                         | 2.60E-10                                      |
| GO:0001525                                      | angiogenesis  | 2.82E-10                                      |
| GO:0005788                                      | endoplasmic reticulum lumen                             | 5.45E-10                                      |
| GO:0030030                                      | cell projection organization                            | 7.93E-09                                      |
| GO:0030863                                      | cortical cytoskeleton                                   | 8.27E-09                                      |
| GO:0031175                                      | neuron projection development                           | 1.06E-08                                      |
| GO:0030168                                      | platelet activation                                     | 1.12E-08                                      |
| GO:0001501                                      | skeletal system development                             | 1.15E-08                                      |
| GO:0048407                                      | platelet-derived growth factor binding                  | 1.16E-08                                      |
| GO:0006897                                      | endocytosis   | 2.12E-08                                      |
| GO:0001503                                      | ossification  | 2.79E-08                                      |
| GO:0030864                                      | cortical actin cytoskeleton                             | 3.42E-08                                      |
| GO:0007229                                      | integrin-mediated signaling pathway                     | 3.71E-08                                      |
| GO:0008201                                      | heparin binding   | 4.25E-08                                      |
| GO:0048585                                      | negative regulation of response to stimulus             | 4.27E-08                                      |
| GO:0003779                                      | actin binding   | 4.30E-08                                      |
| GO:0016049                                      | cell growth   | 4.93E-08                                      |
| GO:0051336                                      | regulation of hydrolase activity                        | 5.56E-08                                      |
| GO:0042330                                      | taxis   | 8.22E-08                                      |
| GO:0022603                                      | regulation of anatomical structure morphogenesis        | 1.58E-07                                      |
| GO:0001101                                      | response to acid chemical                               | 2.02E-07                                      |
| HP:0000006                                      | Autosomal dominant inheritance                          | 6.52E-07                                      |
| GO:0045121                                      | membrane raft   | 7.13E-07                                      |
| GO:0030193                                      | regulation of blood coagulation                         | 1.24E-06                                      |
| GO:0032835                                      | glomerulus development                                  | 1.34E-06                                      |
| GO:0070848                                      | response to growth factor                               | 1.36E-06                                      |
| GO:0051241                                      | negative regulation of multicellular organismal process | 1.52E-06                                      |
| GO:0009887                                      | organ morphogenesis                                     | 2.65E-06                                      |
| HP:0000541                                      | Retinal detachment                                      | 4.93E-06                                      |
| HP:0001388                                      | Joint laxity  | 5.14E-06                                      |
| GO:0061134                                      | peptidase regulator activity                            | 5.62E-06                                      |
| HP:0005111                                      | Dilatation of the ascending aorta                       | 6.62E-06                                      |
| GO:0050840                                      | extracellular matrix binding                            | 7.01E-06                                      |
| HP:0000015                                      | Bladder diverticulum                                    | 1.11E-05                                      |
| HP:0002645                                      | Wormian bones   | 1.28E-05                                      |

|            |  |          |
|------------|--|----------|
| GO:0009968 | negative regulation of signal transduction             | 1.79E-05 |
| GO:0046903 | secretion  | 1.84E-05 |
| HP:0000938 | Osteopenia   | 2.11E-05 |
| GO:0061448 | connective tissue development                          | 2.32E-05 |
| GO:0008285 | negative regulation of cell proliferation              | 2.77E-05 |
| GO:0009897 | external side of plasma membrane                       | 3.03E-05 |
| GO:0044853 | plasma membrane raft                                   | 3.67E-05 |
| HP:0001892 | Abnormal bleeding                                      | 3.86E-05 |
| GO:0051345 | positive regulation of hydrolase activity              | 4.13E-05 |
| GO:0031091 | platelet alpha granule                                 | 4.53E-05 |
| GO:0006027 | glycosaminoglycan catabolic process                    | 4.53E-05 |
| GO:0071495 | cellular response to endogenous stimulus               | 4.61E-05 |
| GO:0051130 | positive regulation of cellular component organization | 5.87E-05 |
| HP:0002797 | Osteolysis   | 5.91E-05 |
| GO:0005044 | scavenger receptor activity                            | 6.32E-05 |
| HP:0001788 | Premature rupture of membranes                         | 7.49E-05 |
| GO:0048771 | tissue remodeling                                      | 8.29E-05 |
| GO:0044273 | sulfur compound catabolic process                      | 8.59E-05 |
| GO:0031226 | intrinsic component of plasma membrane                 | 8.86E-05 |
| GO:0009967 | positive regulation of signal transduction             | 9.80E-05 |
| GO:0007264 | small GTPase mediated signal transduction              | 0.000103 |
| GO:0071230 | cellular response to amino acid stimulus               | 0.000111 |
| GO:0005796 | Golgi lumen  | 0.00012  |
| GO:0070208 | protein heterotrimerization                            | 0.000126 |
| GO:0009415 | response to water                                      | 0.000135 |
| HP:0000977 | Soft skin  | 0.000137 |
| HP:0001073 | Cigarette-paper scars                                  | 0.000175 |
| GO:0060284 | regulation of cell development                         | 0.000176 |
| HP:0001633 | Abnormality of the mitral valve                        | 0.000187 |
| GO:0052547 | regulation of peptidase activity                       | 0.000195 |
| GO:0072376 | protein activation cascade                             | 0.000205 |
| GO:0051093 | negative regulation of developmental process           | 0.000242 |
| HP:0004415 | Pulmonary artery stenosis                              | 0.000315 |
| GO:0060485 | mesenchyme development                                 | 0.000315 |
| HP:0003549 | Abnormality of connective tissue                       | 0.000323 |
| HP:0000023 | Inguinal hernia  | 0.000328 |
| HP:0000934 | Chondrocalcinosis                                      | 0.000342 |
| GO:0035987 | endodermal cell differentiation                        | 0.000342 |
| GO:2000394 | positive regulation of lamellipodium morphogenesis     | 0.000392 |
| GO:0006024 | glycosaminoglycan biosynthetic process                 | 0.000414 |
| HP:0007502 | Follicular hyperkeratosis                              | 0.000507 |
| HP:0000703 | Dentinogenesis imperfecta                              | 0.000507 |
| HP:0005222 | Bowel diverticulosis                                   | 0.000557 |
| GO:0061073 | ciliary body morphogenesis                             | 0.000679 |
| GO:0007417 | central nervous system development                     | 0.000753 |
| GO:0034329 | cell junction assembly                                 | 0.000812 |
| HP:0006460 | Increased laxity of ankles                             | 0.000879 |
| HP:0006316 | Irregularly spaced teeth                               | 0.000879 |
| HP:0002010 | Narrow maxilla   | 0.000879 |
| HP:0002982 | Tibial bowing  | 0.000923 |
| GO:0005543 | phospholipid binding                                   | 0.000967 |
| GO:0002020 | protease binding                                       | 0.00109  |
| GO:0060429 | epithelium development                                 | 0.00117  |
| GO:0006873 | cellular ion homeostasis                               | 0.00122  |
| GO:0001837 | epithelial to mesenchymal transition                   | 0.00142  |
| HP:0004331 | Decreased skull ossification                           | 0.00143  |
| GO:0001968 | fibronectin binding                                    | 0.0015   |
| GO:0060322 | head development                                       | 0.00155  |
| GO:0031093 | platelet alpha granule lumen                           | 0.00155  |
| GO:0045807 | positive regulation of endocytosis                     | 0.00161  |
| GO:0031253 | cell projection membrane                               | 0.00169  |
| GO:0050673 | epithelial cell proliferation                          | 0.00189  |
| GO:0044091 | membrane biogenesis                                    | 0.00199  |
| GO:0007009 | plasma membrane organization                           | 0.00199  |
| GO:0019904 | protein domain specific binding                        | 0.00242  |
| GO:0031579 | membrane raft organization                             | 0.00243  |

|            |   |         |
|------------|---|---------|
| GO:0042383 | sarcolemma  | 0.00249 |
| GO:0031947 | negative regulation of glucocorticoid biosynthetic process            | 0.00263 |
| GO:0031944 | negative regulation of glucocorticoid metabolic process               | 0.00263 |
| GO:0005017 | platelet-derived growth factor-activated receptor activity            | 0.00263 |
| GO:0070613 | regulation of protein processing                                      | 0.00278 |
| HP:0000765 | Abnormality of the thorax   | 0.00298 |
| GO:0030898 | actin-dependent ATPase activity                                       | 0.00298 |
| GO:0043202 | lysosomal lumen   | 0.00299 |
| HP:0002579 | Gastrointestinal dysmotility  | 0.00315 |
| GO:0038096 | Fc-gamma receptor signaling pathway involved in phagocytosis          | 0.00339 |
| HP:0005988 | Congenital muscular torticollis                                       | 0.00341 |
| HP:0005758 | Basilar impression  | 0.00341 |
| GO:0002682 | regulation of immune system process                                   | 0.00354 |
| GO:0048306 | calcium-dependent protein binding                                     | 0.00372 |
| GO:0071295 | cellular response to vitamin  | 0.00468 |
| GO:0048552 | regulation of metalloenzyme activity                                  | 0.0048  |
| GO:0005516 | calmodulin binding  | 0.0048  |
| GO:0018108 | peptidyl-tyrosine phosphorylation                                     | 0.00491 |
| GO:0090132 | epithelium migration  | 0.00495 |
| HP:0012372 | Abnormal eye morphology   | 0.00527 |
| GO:0006954 | inflammatory response   | 0.00544 |
| GO:0060401 | cytosolic calcium ion transport                                       | 0.00571 |
| GO:0050730 | regulation of peptidyl-tyrosine phosphorylation                       | 0.00605 |
| GO:0045177 | apical part of cell   | 0.00618 |
| GO:0043197 | dendritic spine   | 0.00618 |
| GO:0019798 | procollagen-proline dioxygenase activity                              | 0.00638 |
| GO:0030659 | cytoplasmic vesicle membrane  | 0.00644 |
| HP:0000325 | Triangular face   | 0.00767 |
| GO:0007423 | sensory organ development   | 0.00767 |
| GO:0043065 | positive regulation of apoptotic process                              | 0.00787 |
| GO:0048745 | smooth muscle tissue development                                      | 0.00822 |
| HP:0005855 | Multiple prenatal fractures   | 0.00826 |
| HP:0003713 | Muscle fiber necrosis   | 0.00826 |
| HP:0002877 | Nocturnal hypoventilation   | 0.00826 |
| GO:0008284 | positive regulation of cell proliferation                             | 0.0083  |
| HP:0000309 | Abnormality of the midface  | 0.00851 |
| HP:0001083 | Ectopia lentis  | 0.00856 |
| GO:2000377 | regulation of reactive oxygen species metabolic process               | 0.00888 |
| GO:0007204 | positive regulation of cytosolic calcium ion concentration            | 0.0094  |
| GO:0048729 | tissue morphogenesis  | 0.00998 |
| GO:0048608 | reproductive structure development                                    | 0.0104  |
| GO:0061061 | muscle structure development  | 0.0107  |
| GO:0070482 | response to oxygen levels   | 0.0115  |
| HP:0000926 | Platyspondyly   | 0.0117  |
| HP:0008873 | Disproportionate short-limb short stature                             | 0.0121  |
| HP:0000520 | Proptosis   | 0.0122  |
| GO:0072007 | mesangial cell differentiation  | 0.0124  |
| GO:0019898 | extrinsic component of membrane                                       | 0.0132  |
| GO:0060765 | regulation of androgen receptor signaling pathway                     | 0.0134  |
| GO:0021782 | glial cell development  | 0.0134  |
| HP:0001650 | Aortic valve stenosis   | 0.0137  |
| HP:0002586 | Peritonitis   | 0.016   |
| HP:0000655 | Vitreoretinal degeneration  | 0.016   |
| HP:0000394 | Lop ear   | 0.016   |
| GO:1903923 | positive regulation of protein processing in phagocytic vesicle       | 0.0165  |
| GO:1902396 | protein localization to tight junction                                | 0.0165  |
| GO:0086098 | angiotensin-activated signaling pathway involved in heart development | 0.0165  |
| GO:0034684 | integrin alphav-beta5 complex   | 0.0165  |
| GO:0014846 | esophagus smooth muscle contraction                                   | 0.0165  |
| GO:0008459 | chondroitin 6-sulfotransferase activity                               | 0.0165  |
| GO:0001868 | regulation of complement activation, lectin pathway                   | 0.0165  |
| GO:0090218 | positive regulation of lipid kinase activity                          | 0.0168  |
| GO:0043531 | ADP binding   | 0.0168  |
| GO:0044089 | positive regulation of cellular component biogenesis                  | 0.0181  |
| HP:0000272 | Malar flattening  | 0.0186  |
| GO:0043567 | regulation of insulin-like growth factor receptor signaling           | 0.0201  |

|            |  |        |
|------------|--|--------|
| GO:0030674 | protein binding, bridging                                      | 0.0203 |
| GO:1900040 | regulation of interleukin-2 secretion                          | 0.021  |
| GO:0072071 | kidney interstitial fibroblast differentiation                 | 0.021  |
| GO:0046325 | negative regulation of glucose import                          | 0.021  |
| GO:0003184 | pulmonary valve morphogenesis                                  | 0.021  |
| HP:0008780 | Congenital bilateral hip dislocation                           | 0.0213 |
| HP:0006067 | Multiple carpal ossification centers                           | 0.0213 |
| HP:0005897 | Severe osteoporosis  | 0.0213 |
| HP:0002691 | Platybasia   | 0.0213 |
| HP:0001757 | High-frequency sensorineural hearing impairment                | 0.0213 |
| HP:0001149 | Lattice corneal dystrophy                                      | 0.0213 |
| HP:0000362 | Otosclerosis   | 0.0213 |
| GO:2001236 | regulation of extrinsic apoptotic signaling pathway            | 0.0236 |
| HP:0005750 | Contractures of the joints of the lower limbs                  | 0.025  |
| HP:0000963 | Thin skin  | 0.0252 |
| HP:0003741 | Congenital muscular dystrophy                                  | 0.026  |
| GO:0051960 | regulation of nervous system development                       | 0.026  |
| GO:2000811 | negative regulation of anoikis                                 | 0.0265 |
| HP:0002960 | Autoimmunity   | 0.0281 |
| GO:0010562 | positive regulation of phosphorus metabolic process            | 0.0283 |
| HP:0002996 | Limited elbow movement   | 0.0288 |
| GO:0006029 | proteoglycan metabolic process                                 | 0.0293 |
| GO:0048534 | hematopoietic or lymphoid organ development                    | 0.0301 |
| HP:0003077 | Hyperlipidemia   | 0.0304 |
| GO:0070374 | positive regulation of ERK1 and ERK2 cascade                   | 0.0323 |
| GO:0098739 | import across plasma membrane                                  | 0.0325 |
| GO:0061314 | Notch signaling involved in heart development                  | 0.0325 |
| GO:0032060 | bleb assembly  | 0.0325 |
| GO:0021670 | lateral ventricle development                                  | 0.0325 |
| GO:0017187 | peptidyl-glutamic acid carboxylation                           | 0.0325 |
| GO:0005218 | intracellular ligand-gated calcium channel activity            | 0.0325 |
| GO:0004065 | arylsulfatase activity   | 0.0325 |
| HP:0001844 | Abnormality of the hallux                                      | 0.0327 |
| HP:0000260 | Wide anterior fontanel   | 0.0328 |
| HP:0008180 | Mildly elevated creatine phosphokinase                         | 0.0343 |
| HP:0000473 | Torticollis  | 0.0343 |
| GO:0051258 | protein polymerization   | 0.0351 |
| GO:0030246 | carbohydrate binding   | 0.0358 |
| GO:0045428 | regulation of nitric oxide biosynthetic process                | 0.0366 |
| GO:0007568 | aging  | 0.0371 |
| GO:0043235 | receptor complex   | 0.0412 |
| HP:0001799 | Short nail   | 0.0421 |
| HP:0001533 | Slender build  | 0.0421 |
| GO:0003094 | glomerular filtration  | 0.0432 |
| HP:0002715 | Abnormality of the immune system                               | 0.044  |
| GO:0030175 | filopodium   | 0.0451 |
| HP:0000545 | Myopia   | 0.0457 |
| GO:0019216 | regulation of lipid metabolic process                          | 0.0457 |
| GO:0097284 | hepatocyte apoptotic process                                   | 0.0473 |
| GO:0035313 | wound healing, spreading of epidermal cells                    | 0.0473 |
| GO:1902174 | positive regulation of keratinocyte apoptotic process          | 0.0481 |
| GO:0097513 | myosin II filament   | 0.0481 |
| GO:0048251 | elastic fiber assembly   | 0.0481 |
| GO:0008449 | N-acetylglucosamine-6-sulfatase activity                       | 0.0481 |
| GO:0007181 | transforming growth factor beta receptor complex assembly      | 0.0481 |
| GO:0005220 | inositol 1,4,5-trisphosphate-sensitive calcium-release channel | 0.0481 |
| GO:0004992 | platelet activating factor receptor activity                   | 0.0481 |
| GO:0004528 | phosphodiesterase I activity                                   | 0.0481 |
| GO:0002826 | negative regulation of T-helper 1 type immune response         | 0.0481 |
| GO:0004252 | serine-type endopeptidase activity                             | 0.05   |

**Supplementary Table 6d. Module 4 Functional Enrichment.** Gene Ontology and Human Phenotype categories with FDR < 0.05

| Gene Ontology (GO) or Human Phenotype (HP) term | Description  | FDR adjusted P-value<br>(hypergeometric test) |
|---|--|---|
| GO:0044429                                      | mitochondrial part                                     | 2.04E-59                                      |
| GO:0005743                                      | mitochondrial inner membrane                           | 4.08E-53                                      |
| GO:0070124                                      | mitochondrial translational initiation                 | 6.90E-28                                      |
| GO:0070126                                      | mitochondrial translational termination                | 3.24E-25                                      |
| GO:0022904                                      | respiratory electron transport chain                   | 4.95E-24                                      |
| GO:0070469                                      | respiratory chain                                      | 1.36E-19                                      |
| GO:0009205                                      | purine ribonucleoside triphosphate metabolic process   | 3.43E-19                                      |
| GO:0046034                                      | ATP metabolic process                                  | 4.12E-19                                      |
| GO:0000313                                      | organellar ribosome                                    | 3.67E-18                                      |
| GO:0050136                                      | NADH dehydrogenase (quinone) activity                  | 1.16E-13                                      |
| GO:0030964                                      | NADH dehydrogenase complex                             | 7.29E-12                                      |
| GO:0005753                                      | mitochondrial proton-transporting ATP synthase complex | 2.55E-11                                      |
| GO:0003735                                      | structural constituent of ribosome                     | 3.05E-11                                      |
| GO:1990542                                      | mitochondrial transmembrane transport                  | 3.23E-10                                      |
| HP:0004360                                      | Abnormality of acid-base homeostasis                   | 3.18E-09                                      |
| GO:0015078                                      | hydrogen ion transmembrane transporter activity        | 4.76E-09                                      |
| GO:1902600                                      | hydrogen ion transmembrane transport                   | 1.40E-08                                      |
| HP:0001254                                      | Lethargy   | 8.58E-06                                      |
| HP:0003546                                      | Exercise intolerance                                   | 0.000141                                      |
| HP:0001298                                      | Encephalopathy   | 0.000178                                      |
| HP:0002490                                      | Increased CSF lactate                                  | 0.000232                                      |
| HP:0002878                                      | Respiratory failure                                    | 0.000253                                      |
| HP:0001427                                      | Mitochondrial inheritance                              | 0.000268                                      |
| HP:0003287                                      | Abnormality of mitochondrial metabolism                | 0.000435                                      |
| HP:0004481                                      | Progressive macrocephaly                               | 0.000597                                      |
| GO:0018065                                      | protein-cofactor linkage                               | 0.00101                                       |
| HP:0000543                                      | Optic disc pallor                                      | 0.00203                                       |
| GO:0070585                                      | protein localization to mitochondrion                  | 0.00238                                       |
| GO:0051536                                      | iron-sulfur cluster binding                            | 0.00301                                       |
| GO:0016226                                      | iron-sulfur cluster assembly                           | 0.00324                                       |
| GO:0004129                                      | cytochrome-c oxidase activity                          | 0.00603                                       |
| HP:0002181                                      | Cerebral edema   | 0.00686                                       |
| HP:0001639                                      | Hypertrophic cardiomyopathy                            | 0.0108  |
| HP:0002415                                      | Leukodystrophy   | 0.0165  |
| GO:0032981                                      | mitochondrial respiratory chain complex I assembly     | 0.0242  |
| GO:1990617                                      | CHOP-ATF4 complex                                      | 0.0307  |
| GO:0016838                                      | carbon-oxygen lyase activity, acting on phosphates     | 0.0307  |
| HP:0001423                                      | X-linked dominant inheritance                          | 0.0427  |
| HP:0000618                                      | Blindness  | 0.0432  |
| GO:0043522                                      | leucine zipper domain binding                          | 0.0487  |
| HP:0001133                                      | Constricted visual fields                              | 0.05  |

**Supplementary Table 6e. Module 6 Functional Enrichment.** Gene Ontology and Human Phenotype categories with FDR < 0.05

| Gene Ontology (GO) or<br>Human Phenotype (HP) term | Description  | FDR adjusted P-value<br>(hypergeometric test) |
|--|--|---|
| GO:0016023   | cytoplasmic membrane-bounded vesicle               | 5.82E-06                                      |
| GO:0040012   | regulation of locomotion                           | 1.86E-05                                      |
| GO:0036500   | ATF6-mediated unfolded protein response            | 5.80E-05                                      |
| GO:0006897   | endocytosis  | 6.96E-05                                      |
| GO:0045121   | membrane raft                                      | 7.81E-05                                      |
| GO:0070161   | anchoring junction                                 | 0.000364                                      |
| GO:2000145   | regulation of cell motility                        | 0.000366                                      |
| GO:0034975   | protein folding in endoplasmic reticulum           | 0.000429                                      |
| GO:0098602   | single organism cell adhesion                      | 0.00044                                       |
| GO:0002699   | positive regulation of immune effector process     | 0.000477                                      |
| GO:0046718   | viral entry into host cell                         | 0.000946                                      |
| GO:0030659   | cytoplasmic vesicle membrane                       | 0.00101                                       |
| HP:0000095   | Abnormality of the glomerulus                      | 0.00142                                       |
| GO:0034097   | response to cytokine                               | 0.00163                                       |
| HP:0012379   | Abnormal enzyme/coenzyme activity                  | 0.00209                                       |
| GO:0007264   | small GTPase mediated signal transduction          | 0.00291                                       |
| GO:0032270   | positive regulation of cellular protein metabolic  | 0.00293                                       |
| GO:0050839   | cell adhesion molecule binding                     | 0.00338                                       |
| GO:0010008   | endosome membrane                                  | 0.00364                                       |
| GO:0098552   | side of membrane                                   | 0.00375                                       |
| HP:0005339   | Abnormality of complement system                   | 0.00383                                       |
| GO:0050211   | procollagen galactosyltransferase activity         | 0.00393                                       |
| GO:0005788   | endoplasmic reticulum lumen                        | 0.00487                                       |
| HP:0002756   | Pathologic fracture                                | 0.00647                                       |
| GO:0009986   | cell surface                                       | 0.00685                                       |
| GO:0007568   | aging  | 0.00696                                       |
| GO:0005178   | integrin binding                                   | 0.00866                                       |
| HP:0002645   | Wormian bones                                      | 0.00874                                       |
| GO:0006098   | pentose-phosphate shunt                            | 0.00891                                       |
| HP:0000467   | Neck muscle weakness                               | 0.01  |
| HP:0008944   | Distal lower limb amyotrophy                       | 0.01  |
| HP:0000418   | Narrow nasal ridge                                 | 0.01  |
| HP:0005474   | Decreased calvarial ossification                   | 0.01  |
| GO:0032880   | regulation of protein localization                 | 0.0102  |
| HP:0000100   | Nephrotic syndrome                                 | 0.0111  |
| HP:0002703   | Abnormality of skull ossification                  | 0.0114  |
| GO:0042270   | protection from natural killer cell mediated cyto  | 0.0117  |
| GO:0010562   | positive regulation of phosphorus metabolic pro    | 0.012   |
| GO:0031625   | ubiquitin protein ligase binding                   | 0.0139  |
| HP:0007394   | Prominent superficial blood vessels                | 0.0139  |
| HP:0000455   | Broad nasal tip                                    | 0.0146  |
| GO:0031399   | regulation of protein modification process         | 0.0148  |
| HP:0000248   | Brachycephaly                                      | 0.016   |
| HP:0000520   | Proptosis  | 0.017   |
| HP:0000774   | Narrow chest                                       | 0.0172  |
| GO:0042269   | regulation of natural killer cell mediated cytotox | 0.018   |
| HP:0004944   | Cerebral aneurysm                                  | 0.0184  |
| HP:0000764   | Peripheral axonal degeneration                     | 0.0184  |
| HP:0002754   | Osteomyelitis                                      | 0.0225  |
| GO:0019322   | pentose biosynthetic process                       | 0.0232  |
| GO:0042296   | ISG15 transferase activity                         | 0.0232  |
| GO:0004619   | phosphoglycerate mutase activity                   | 0.0232  |
| GO:0004083   | bisphosphoglycerate 2-phosphatase activity         | 0.0232  |
| GO:0004082   | bisphosphoglycerate mutase activity                | 0.0232  |
| GO:0048475   | coated membrane                                    | 0.0235  |
| HP:0002185   | Neurofibrillary tangles                            | 0.0235  |
| HP:0001744   | Splenomegaly                                       | 0.0246  |
| GO:0045087   | innate immune response                             | 0.0253  |

|            |   |        |
|------------|---|--------|
| GO:0071363 | cellular response to growth factor stimulus     | 0.0272 |
| GO:0051129 | negative regulation of cellular component organ | 0.0297 |
| HP:0001284 | Areflexia                                       | 0.0307 |
| HP:0009771 | Osteolytic defects of the phalanges of the hand | 0.0354 |
| HP:0002813 | Abnormality of limb bone morphology             | 0.0376 |
| GO:0007229 | integrin-mediated signaling pathway             | 0.0402 |
| GO:0097190 | apoptotic signaling pathway                     | 0.0414 |
| HP:0000605 | Supranuclear gaze palsy                         | 0.0421 |
| GO:0048585 | negative regulation of response to stimulus     | 0.0481 |
| HP:0002679 | Abnormality of the sella turcica                | 0.0494 |
| GO:0042149 | cellular response to glucose starvation         | 0.05   |
| CORUM:1223 | H2AX complex, isolated from cells without IR ex | 0.05   |

**Supplementary Table 6f. Module 11 Functional Enrichment.** Gene Ontology and Human Phenotype categories with FDR < 0.05

| Gene Ontology (GO) or Human Phenotype (HP) term | Description  | FDR adjusted P-value (hypergeometric test) |
|---|--|--|
| GO:0006954                                      | inflammatory response  | 2.41E-08                                   |
| GO:0050776                                      | regulation of immune response                                      | 2.95E-08                                   |
| GO:0045087                                      | innate immune response   | 3.00E-08                                   |
| GO:0001816                                      | cytokine production  | 4.52E-08                                   |
| GO:0030334                                      | regulation of cell migration                                       | 4.21E-07                                   |
| GO:0002252                                      | immune effector process  | 7.36E-07                                   |
| GO:1903557                                      | positive regulation of tumor necrosis factor signaling             | 6.84E-06                                   |
| GO:0006909                                      | phagocytosis   | 1.48E-05                                   |
| GO:0002274                                      | myeloid leukocyte activation                                       | 1.50E-05                                   |
| GO:0014068                                      | positive regulation of phosphatidylinositol 3-kinase activity      | 1.58E-05                                   |
| GO:0030595                                      | leukocyte chemotaxis   | 1.69E-05                                   |
| GO:0006911                                      | phagocytosis, engulfment   | 1.92E-05                                   |
| HP:0005356                                      | Decreased serum complement factor I                                | 2.34E-05                                   |
| GO:0072376                                      | protein activation cascade   | 3.96E-05                                   |
| HP:0000793                                      | Membranoproliferative glomerulonephritis                           | 5.82E-05                                   |
| GO:0002573                                      | myeloid leukocyte differentiation                                  | 6.74E-05                                   |
| GO:0097190                                      | apoptotic signaling pathway  | 9.61E-05                                   |
| GO:0030036                                      | actin cytoskeleton organization                                    | 0.000103                                   |
| GO:0008360                                      | regulation of cell shape   | 0.000108                                   |
| GO:0005602                                      | complement component C1 complex                                    | 0.000182                                   |
| GO:0002250                                      | adaptive immune response   | 0.000191                                   |
| GO:0006956                                      | complement activation  | 0.000216                                   |
| GO:0070661                                      | leukocyte proliferation  | 0.000269                                   |
| GO:0045807                                      | positive regulation of endocytosis                                 | 0.000292                                   |
| GO:0046427                                      | positive regulation of JAK-STAT cascade                            | 0.000338                                   |
| GO:0030041                                      | actin filament polymerization                                      | 0.000352                                   |
| GO:0030155                                      | regulation of cell adhesion  | 0.000643                                   |
| HP:0002725                                      | Systemic lupus erythematosus                                       | 0.000685                                   |
| GO:0050715                                      | positive regulation of cytokine secretion                          | 0.000786                                   |
| GO:0007169                                      | transmembrane receptor protein tyrosine kinase signaling pathway   | 0.00101                                    |
| GO:0051247                                      | positive regulation of protein metabolic process                   | 0.00102                                    |
| GO:0043552                                      | positive regulation of phosphatidylinositol 3-kinase activity      | 0.00105                                    |
| GO:0031347                                      | regulation of defense response                                     | 0.00107                                    |
| HP:0200098                                      | Absent skin pigmentation   | 0.00108                                    |
| HP:0007544                                      | Piebaldism   | 0.00108                                    |
| GO:0097169                                      | AIM2 inflammasome complex  | 0.00108                                    |
| GO:0009617                                      | response to bacterium  | 0.00115                                    |
| GO:0006775                                      | fat-soluble vitamin metabolic process                              | 0.00122                                    |
| GO:0071222                                      | cellular response to lipopolysaccharide                            | 0.00133                                    |
| GO:0009986                                      | cell surface   | 0.00137                                    |
| GO:0072559                                      | NLRP3 inflammasome complex   | 0.0018                                     |
| GO:0042327                                      | positive regulation of phosphorylation                             | 0.00196                                    |
| GO:0030833                                      | regulation of actin filament polymerization                        | 0.00199                                    |
| GO:0043303                                      | mast cell degranulation  | 0.00234                                    |
| GO:0032762                                      | mast cell cytokine production                                      | 0.00269                                    |
| GO:0016892                                      | endoribonuclease activity, producing 3'-phosphorylated nucleotides | 0.00269                                    |
| GO:0009611                                      | response to wounding   | 0.00269                                    |
| GO:0042531                                      | positive regulation of tyrosine phosphorylation                    | 0.00293                                    |
| GO:0005773                                      | vacuole  | 0.00392                                    |
| GO:0007229                                      | integrin-mediated signaling pathway                                | 0.00408                                    |
| GO:0031529                                      | ruffle organization  | 0.00436                                    |
| GO:0042362                                      | fat-soluble vitamin biosynthetic process                           | 0.00498                                    |
| GO:0043085                                      | positive regulation of catalytic activity                          | 0.00596                                    |
| GO:0031953                                      | negative regulation of protein autophosphorylation                 | 0.00638                                    |
| HP:0007443                                      | Partial albinism   | 0.00644                                    |
| GO:0038024                                      | cargo receptor activity  | 0.00724                                    |
| GO:0019369                                      | arachidonic acid metabolic process                                 | 0.00781                                    |
| GO:0044130                                      | negative regulation of growth of symbiont in host cell             | 0.00794                                    |
| GO:0048011                                      | neurotrophin TRK receptor signaling pathway                        | 0.00894                                    |
| GO:0034097                                      | response to cytokine   | 0.0113                                     |

|            |   |        |
|------------|---|--------|
| GO:0005092 | GDP-dissociation inhibitor activity   | 0.0116 |
| GO:0043069 | negative regulation of programmed cell death  | 0.0123 |
| GO:0032103 | positive regulation of response to external stimulus                                  | 0.0124 |
| GO:0048872 | homeostasis of number of cells  | 0.0141 |
| GO:0001891 | phagocytic cup  | 0.0158 |
| HP:0100523 | Liver abscess   | 0.016  |
| GO:0051241 | negative regulation of multicellular organismal process                               | 0.0161 |
| HP:0001025 | Urticaria   | 0.0174 |
| GO:0042802 | identical protein binding   | 0.0174 |
| GO:0002675 | positive regulation of acute inflammatory response                                    | 0.0182 |
| GO:0019902 | phosphatase binding   | 0.0189 |
| GO:0043372 | positive regulation of CD4-positive, alpha-beta T cell mediated lymphocyte activation | 0.0207 |
| GO:0016505 | peptidase activator activity involved in apoptosis                                    | 0.0207 |
| HP:0002211 | White forelock  | 0.0223 |
| HP:0000727 | Frontal lobe dementia   | 0.0223 |
| GO:0043065 | positive regulation of apoptotic process  | 0.0243 |
| GO:1903409 | reactive oxygen species biosynthetic process  | 0.0256 |
| GO:0004540 | ribonuclease activity   | 0.0256 |
| HP:0000421 | Epistaxis   | 0.031  |
| GO:0030141 | secretory granule   | 0.0311 |
| GO:0005581 | collagen trimer   | 0.0322 |
| GO:1990682 | CSF1-CSF1R complex  | 0.033  |
| GO:1990246 | uniplex complex   | 0.033  |
| GO:1900387 | negative regulation of cell-cell adhesion by neuregulin                               | 0.033  |
| GO:0071718 | sodium-independent icosanoid transport  | 0.033  |
| GO:0070976 | TIR domain binding  | 0.033  |
| GO:0051022 | Rho GDP-dissociation inhibitor binding  | 0.033  |
| GO:0050783 | cocaine metabolic process   | 0.033  |
| GO:0043376 | regulation of CD8-positive, alpha-beta T cell mediated lymphocyte activation          | 0.033  |
| GO:0038162 | erythropoietin-mediated signaling pathway   | 0.033  |
| GO:0035921 | desmosome disassembly   | 0.033  |
| GO:0035509 | negative regulation of myosin-light-chain-phonemediated signaling pathway             | 0.033  |
| GO:0034988 | Fc-gamma receptor I complex binding   | 0.033  |
| GO:0030421 | defecation  | 0.033  |
| GO:0017024 | myosin I binding  | 0.033  |
| GO:0014739 | positive regulation of muscle hyperplasia   | 0.033  |
| GO:0014016 | neuroblast differentiation  | 0.033  |
| GO:0005121 | Toll binding  | 0.033  |
| GO:0005020 | stem cell factor receptor activity  | 0.033  |
| GO:0005011 | macrophage colony-stimulating factor receptor activity                                | 0.033  |
| GO:0004796 | thromboxane-A synthase activity   | 0.033  |
| GO:0002930 | trabecular meshwork development   | 0.033  |
| GO:1900026 | positive regulation of substrate adhesion-dependent cell migration                    | 0.0356 |
| GO:0045730 | respiratory burst   | 0.0356 |
| GO:0050795 | regulation of behavior  | 0.0363 |
| GO:0030027 | lamellipodium   | 0.0383 |
| GO:0090501 | RNA phosphodiester bond hydrolysis  | 0.0397 |
| GO:0002431 | Fc receptor mediated stimulatory signaling pathway                                    | 0.0413 |
| GO:0060071 | Wnt signaling pathway, planar cell polarity pathway                                   | 0.0426 |
| GO:0031225 | anchored component of membrane  | 0.0464 |
| HP:0002354 | Memory impairment   | 0.05   |

**Supplementary Table 6g. Module 17 Functional Enrichment.** Gene Ontology and Human Phenotype categories with FDR < 0.05

| Gene Ontology (GO) or Human Phenotype (HP) term | Description   | FDR adjusted P-value (hypergeometric test) |
|---|---|--|
| GO:0035295                                      | tube development  | 6.40E-10                                   |
| GO:0001525                                      | angiogenesis  | 2.07E-09                                   |
| GO:0048568                                      | embryonic organ development                                     | 2.52E-08                                   |
| GO:0003007                                      | heart morphogenesis   | 3.07E-08                                   |
| GO:0016477                                      | cell migration  | 2.08E-07                                   |
| GO:0090132                                      | epithelium migration  | 2.54E-07                                   |
| GO:0009855                                      | determination of bilateral symmetry                             | 8.60E-07                                   |
| GO:0001947                                      | heart looping   | 1.18E-06                                   |
| GO:0045165                                      | cell fate commitment  | 0.000107                                   |
| GO:0001822                                      | kidney development  | 0.000301                                   |
| HP:0001901                                      | Polycythemia  | 0.000371                                   |
| GO:0007386                                      | compartment pattern specification                               | 0.000473                                   |
| GO:0001666                                      | response to hypoxia   | 0.000483                                   |
| GO:0030324                                      | lung development  | 0.000682                                   |
| GO:0048738                                      | cardiac muscle tissue development                               | 0.000781                                   |
| GO:0045668                                      | negative regulation of osteoblast differentiation               | 0.000796                                   |
| GO:0001974                                      | blood vessel remodeling   | 0.000796                                   |
| GO:0050673                                      | epithelial cell proliferation                                   | 0.000802                                   |
| GO:0045765                                      | regulation of angiogenesis                                      | 0.000951                                   |
| GO:0021700                                      | developmental maturation  | 0.00122                                    |
| GO:0048663                                      | neuron fate commitment  | 0.00131                                    |
| GO:1903707                                      | negative regulation of hemopoiesis                              | 0.00142                                    |
| GO:0007155                                      | cell adhesion   | 0.00153                                    |
| GO:0040012                                      | regulation of locomotion  | 0.00154                                    |
| GO:0033002                                      | muscle cell proliferation                                       | 0.00263                                    |
| GO:0048711                                      | positive regulation of astrocyte differentiation                | 0.00281                                    |
| HP:0004936                                      | Venous thrombosis   | 0.0029                                     |
| GO:0031226                                      | intrinsic component of plasma membrane                          | 0.00338                                    |
| GO:0009611                                      | response to wounding  | 0.00346                                    |
| GO:0070986                                      | left/right axis specification                                   | 0.0035                                     |
| GO:0030334                                      | regulation of cell migration                                    | 0.00363                                    |
| GO:0048715                                      | negative regulation of oligodendrocyte differentiation          | 0.00427                                    |
| HP:0002624                                      | Venous abnormality  | 0.00456                                    |
| GO:0051094                                      | positive regulation of developmental process                    | 0.00498                                    |
| GO:0051240                                      | positive regulation of multicellular organismal process         | 0.00537                                    |
| GO:0019199                                      | transmembrane receptor protein kinase activity                  | 0.0063                                     |
| GO:0045649                                      | regulation of macrophage differentiation                        | 0.00702                                    |
| GO:0030900                                      | forebrain development   | 0.00713                                    |
| GO:0008285                                      | negative regulation of cell proliferation                       | 0.00729                                    |
| GO:0009967                                      | positive regulation of signal transduction                      | 0.00774                                    |
| GO:0097150                                      | neuronal stem cell maintenance                                  | 0.00808                                    |
| GO:0006182                                      | cGMP biosynthetic process                                       | 0.00808                                    |
| GO:0061138                                      | morphogenesis of a branching epithelium                         | 0.00922                                    |
| GO:0048863                                      | stem cell differentiation                                       | 0.0119                                     |
| GO:0000122                                      | negative regulation of transcription from RNA polymerase II prc | 0.0119                                     |
| GO:0061384                                      | heart trabecula morphogenesis                                   | 0.013                                      |
| GO:0007220                                      | Notch receptor processing                                       | 0.013                                      |
| GO:0005912                                      | adherens junction   | 0.0139                                     |
| GO:0048545                                      | response to steroid hormone                                     | 0.0143                                     |
| GO:0032102                                      | negative regulation of response to external stimulus            | 0.0143                                     |
| GO:0042491                                      | auditory receptor cell differentiation                          | 0.0145                                     |
| GO:0008284                                      | positive regulation of cell proliferation                       | 0.0146                                     |
| HP:0011029                                      | Internal hemorrhage   | 0.0151                                     |
| GO:0045121                                      | membrane raft   | 0.0164                                     |
| GO:0048566                                      | embryonic digestive tract development                           | 0.0175                                     |
| GO:0046875                                      | ephrin receptor binding   | 0.0175                                     |
| HP:0002040                                      | Esophageal varix  | 0.018                                      |
| GO:1901222                                      | regulation of NIK/NF-kappaB signaling                           | 0.0191                                     |
| GO:0045777                                      | positive regulation of blood pressure                           | 0.0191                                     |

|            |  |        |
|------------|--|--------|
| GO:0009925 | basal plasma membrane  | 0.0191 |
| GO:0030513 | positive regulation of BMP signaling pathway                       | 0.0208 |
| GO:0060412 | ventricular septum morphogenesis                                   | 0.0226 |
| GO:0045604 | regulation of epidermal cell differentiation                       | 0.0226 |
| GO:2001200 | positive regulation of dendritic cell differentiation              | 0.0237 |
| GO:2000637 | positive regulation of gene silencing by miRNA                     | 0.0237 |
| GO:0085018 | maintenance of symbiont-containing vacuole by host                 | 0.0237 |
| GO:0071931 | positive regulation of transcription involved in G1/S transition o | 0.0237 |
| GO:0071288 | cellular response to mercury ion                                   | 0.0237 |
| GO:0060843 | venous endothelial cell differentiation                            | 0.0237 |
| GO:0046878 | positive regulation of saliva secretion                            | 0.0237 |
| GO:0035379 | carbon dioxide transmembrane transporter activity                  | 0.0237 |
| GO:0035378 | carbon dioxide transmembrane transport                             | 0.0237 |
| GO:0035377 | transepithelial water transport                                    | 0.0237 |
| GO:0030184 | nitric oxide transmembrane transporter activity                    | 0.0237 |
| GO:0003270 | Notch signaling pathway involved in regulation of secondary he     | 0.0237 |
| GO:0043066 | negative regulation of apoptotic process                           | 0.0287 |
| GO:0050999 | regulation of nitric-oxide synthase activity                       | 0.0303 |
| GO:1903507 | negative regulation of nucleic acid-templated transcription        | 0.0316 |
| HP:0001342 | Cerebral hemorrhage  | 0.0361 |
| HP:0001048 | Cavernous hemangioma   | 0.0416 |
| GO:0045600 | positive regulation of fat cell differentiation                    | 0.0439 |
| GO:0043392 | negative regulation of DNA binding                                 | 0.0463 |
| GO:2001027 | negative regulation of endothelial cell chemotaxis                 | 0.0474 |
| GO:1902263 | apoptotic process involved in embryonic digit morphogenesis        | 0.0474 |
| GO:0098507 | polynucleotide 5' dephosphorylation                                | 0.0474 |
| GO:0090164 | asymmetric Golgi ribbon formation                                  | 0.0474 |
| GO:0072563 | endothelial microparticle  | 0.0474 |
| GO:0061030 | epithelial cell differentiation involved in mammary gland alveoli  | 0.0474 |
| GO:0060352 | cell adhesion molecule production                                  | 0.0474 |
| GO:0048866 | stem cell fate specification                                       | 0.0474 |
| GO:0036273 | response to statin   | 0.0474 |
| GO:0035799 | ureter maturation  | 0.0474 |
| GO:0035331 | negative regulation of hippo signaling                             | 0.0474 |
| GO:0034617 | tetrahydrobiopterin binding  | 0.0474 |
| GO:0030950 | establishment or maintenance of actin cytoskeleton polarity        | 0.0474 |
| GO:0021894 | cerebral cortex GABAergic interneuron development                  | 0.0474 |
| GO:0021830 | interneuron migration from the subpallium to the cortex            | 0.0474 |
| GO:0020003 | symbiont-containing vacuole  | 0.0474 |
| GO:0018262 | isopeptide cross-linking   | 0.0474 |
| GO:0014806 | smooth muscle hyperplasia  | 0.0474 |
| GO:0014740 | negative regulation of muscle hyperplasia                          | 0.0474 |
| GO:0004651 | polynucleotide 5'-phosphatase activity                             | 0.0474 |
| GO:0004517 | nitric-oxide synthase activity                                     | 0.0474 |
| GO:0003192 | mitral valve formation   | 0.0474 |
| GO:0001300 | chronological cell aging   | 0.0474 |
| GO:0007163 | establishment or maintenance of cell polarity                      | 0.0488 |
| GO:0007167 | enzyme linked receptor protein signaling pathway                   | 0.0497 |

**Supplemental Table 7a: Module 1 transcription factor binding site (TFBS) overrepresentation analysis.**

Results with Fisher score  $\geq 7$  and Z-score  $\geq 10$  shown

| TFBS   | JASPAR ID | Z-score | Fisher score |
|--------|-----------|---------|--------------|
| MEF2A  | MA0052.1  | 14.385  | 20.368       |
| RORA_1 | MA0071.1  | 12.51   | 17.763       |
| NR4A2  | MA0160.1  | 10.25   | 15.888       |
| Esrrb  | MA0141.1  | 11.952  | 15.139       |
| HNF4A  | MA0114.1  | 10.266  | 9.604        |

**Supplemental Table 7b: Module 2 transcription factor binding site (TFBS) overrepresentation analysis.**

Results with Fisher score >= 7 and Z-score >= 10 shown

| TFBS  | JASPAR ID | Z-score | Fisher score |
|-------|-----------|---------|--------------|
| GABPA | MA0062.2  | 11.195  | 9.003        |

Supplemental Data 7c: mod 3 transcription factor binding site (TFBS) overrepresentation analysis.

**Supplemental Table 7c: Module 3 transcription factor binding site (TFBS) overrepresentation analysis.**

Results with Fisher score >= 7 and Z-score >= 10 shown

| TFBS   | JASPAR ID | Z-score | Fisher score |
|--------|-----------|---------|--------------|
| TEAD1  | MA0090.1  | 16.06   | 20.748       |
| HOXA5  | MA0158.1  | 28.527  | 18.847       |
| SPI1   | MA0080.2  | 14.121  | 18.634       |
| RUNX1  | MA0002.2  | 21.493  | 18.143       |
| NFATC2 | MA0152.1  | 23.135  | 17.052       |
| STAT1  | MA0137.2  | 15.012  | 16.347       |
| FEV    | MA0156.1  | 14.803  | 16.091       |
| CEBPA  | MA0102.2  | 18.63   | 15.788       |
| FOXO3  | MA0157.1  | 19.586  | 15.289       |
| ELF5   | MA0136.1  | 20.4    | 15.006       |
| SRY    | MA0084.1  | 17.844  | 14.994       |
| SOX9   | MA0077.1  | 16.859  | 14.378       |
| Foxa2  | MA0047.2  | 17.228  | 14.11        |
| FOXA1  | MA0148.1  | 25.226  | 14.013       |
| Prrx2  | MA0075.1  | 14.274  | 13.669       |
| Gfi    | MA0038.1  | 18.076  | 13.66        |
| Sox5   | MA0087.1  | 12.409  | 12.761       |
| Pdx1   | MA0132.1  | 19.284  | 12.534       |
| Nobox  | MA0125.1  | 18.448  | 12.222       |
| SPIB   | MA0081.1  | 14.152  | 12.132       |

|               |          |        |        |
|---------------|----------|--------|--------|
| Hand1::Tcfe2a | MA0092.1 | 17.801 | 12.028 |
| FOXI1         | MA0042.1 | 16.889 | 11.279 |
| FOXD1         | MA0031.1 | 16.83  | 10.767 |
| Foxd3         | MA0041.1 | 16.79  | 10.706 |
| ARID3A        | MA0151.1 | 15.298 | 10.561 |
| AP1           | MA0099.2 | 13.534 | 10.21  |
| Sox17         | MA0078.1 | 15.28  | 8.818  |
| Nkx2-5        | MA0063.1 | 18.068 | 8.666  |
| Sox2          | MA0143.1 | 10.609 | 8.145  |
| IRF1          | MA0050.1 | 11.417 | 7.737  |
| Ddit3::Cebpa  | MA0019.1 | 12.315 | 7.574  |
| TAL1::TCF3    | MA0091.1 | 12.704 | 7.492  |

**Supplemental Table 7d: Module 6 transcription factor binding site (TFBS) overrepresentation analysis.**

Results with Fisher score  $\geq 7$  and Z-score  $\geq 10$  shown

| TFBS | JASPAR ID | Z-score | Fisher score |
|------|-----------|---------|--------------|
| ELK1 | MA0028.1  | 11.17   | 7.803        |

**Supplemental Table 7e: Module 7 transcription factor binding site (TFBS) overrepresentation analysis.**

Results with Fisher score  $\geq 7$  and Z-score  $\geq 10$  shown

| TFBS        | JASPAR ID | Z-score | Fisher score |
|-------------|-----------|---------|--------------|
| Tal1::Gata1 | MA0140.1  | 16.629  | 10.813       |

**Supplemental Table 7f: Module 17 transcription factor binding site (TFBS) overrepresentation analysis.**

Results with Fisher score  $\geq 7$  and Z-score  $\geq 10$  shown

| TFBS  | JASPAR ID | Z-score | Fisher score |
|-------|-----------|---------|--------------|
| ELK1  | MA0028.1  | 17.646  | 10.238       |
| INSM1 | MA0155.1  | 14.577  | 9.455        |
| Zfx   | MA0146.1  | 13.328  | 8.785        |
| Klf4  | MA0039.2  | 20.059  | 7.999        |

**Supplemental Data 8a: Conservation of Modules across Human Data**

**Sets.** Zsummary < 2 implies no evidence for module preservation,  
2 < Zsummary < 10 implies weak evidence of preservation and  
Zsummary >10 implies strong evidence for module preservation.

| Module | Module Size | Z Summary |
|--------|-------------|-----------|
| 0      | 1000        | 0.354     |
| 1      | 539         | 27.1      |
| 2      | 502         | 26        |
| 3      | 398         | 8.64      |
| 4      | 267         | 4.32      |
| 5      | 88          | 1.94      |
| 6      | 110         | 6.81      |
| 7      | 60          | 1.73      |
| 8      | 65          | 4.35      |
| 9      | 37          | 2.25      |
| 10     | 63          | 8.98      |
| 11     | 47          | 6.08      |
| 12     | 37          | 2.14      |
| 13     | 36          | 0.633     |
| 14     | 29          | 2.88      |
| 15     | 33          | 2.63      |
| 16     | 7           | 0.796     |
| 17     | 33          | 0.934     |

**Supplemental Data 8b: Conservation of Modules across Species (human and procine Data Sets).** Zsummary < 2 implies no evidence for module preservation, 2 < Zsummary < 10 implies weak evidence of preservation and Zsummary >10 implies strong evidence for module preservation.

| Module | Module size | Z Summary |
|--------|-------------|-----------|
| 0      | 1000        | 1.84      |
| 1      | 539         | 14.8      |
| 2      | 502         | 5.57      |
| 3      | 398         | 9.47      |
| 4      | 267         | 7.68      |
| 5      | 88          | 3.05      |
| 6      | 110         | 3.11      |
| 7      | 60          | 0.445     |
| 8      | 65          | 3.4       |
| 9      | 37          | 5.43      |
| 10     | 63          | 6.14      |
| 11     | 47          | 6.27      |
| 12     | 37          | 4.35      |
| 13     | 36          | -0.512    |
| 14     | 29          | 1.1       |
| 15     | 33          | 3.52      |
| 16     | 7           | 0.868     |
| 17     | 33          | 3.71      |

**Supplemental Data 8c: Association of module eigengene with disease status.** Human sepsis with multi-organ dysfunction vs controls

| Module | Coefficient  | P-value<br>(FDR adjusted) |
|--------|--------------|---------------------------|
| 0      | 0.380067967  | 1.37E-06                  |
| 1      | -0.370028149 | 4.52E-06                  |
| 2      | 0.378967138  | 1.58E-06                  |
| 3      | -0.314635576 | 0.000409186               |
| 4      | -0.367401006 | 6.02E-06                  |
| 5      | -0.361177786 | 1.14E-05                  |
| 6      | 0.375370487  | 2.45E-06                  |
| 7      | 0.301751322  | 0.000858479               |
| 8      | 0.34711512   | 4.07E-05                  |
| 9      | 0.362842149  | 9.64E-06                  |
| 10     | 0.390928695  | 3.00E-07                  |
| 11     | -0.131472079 | 0.198079441               |
| 12     | -0.096027896 | 0.352299397               |
| 13     | 0.361703691  | 1.08E-05                  |
| 14     | 0.352482276  | 2.56E-05                  |
| 15     | 0.395542961  | 1.43E-07                  |
| 16     | -0.232150298 | 0.016489467               |
| 17     | -0.308515369 | 0.000587722               |

**Supplemental Data 8d: Association of module eigengene values with disease status.** Porcine model of ICUAW Day 5 sepsis vs Day 1 control

| Module | Coefficient  | P-value<br>(FDR adjusted) |
|--------|--------------|---------------------------|
| 0      | 0.342010933  | 0                         |
| 1      | -0.343470633 | 2.22E-15                  |
| 2      | 0.362021015  | 0                         |
| 3      | -0.238452868 | 0.004122182               |
| 4      | -0.320736172 | 9.99E-16                  |
| 5      | -0.30230668  | 1.75E-08                  |
| 6      | 0.163683402  | 0.036778161               |
| 7      | -0.272556578 | 5.30E-06                  |
| 8      | 0.424086818  | 0                         |
| 9      | 0.427822514  | 0                         |
| 10     | 0.358892396  | 0                         |
| 11     | 0.042444773  | 0.697227349               |
| 12     | -0.231994183 | 0.018551701               |
| 13     | -0.381391573 | 0                         |
| 14     | 0.327734961  | 0                         |
| 15     | 0.301133419  | 7.08E-09                  |
| 16     | -0.022019174 | 0.809482794               |
| 17     | -0.224111232 | 0.002619171               |